DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PUBLIC MEETING:

PRESCRIPTION DRUG USER FEE ACT (PDUFA)

9:07 a.m. to 2:36 p.m.

Friday, December 7, 2001

Hyatt Regency

Bethesda, Maryland

C O N T E N T S

P R O C E E D I N G S

[9:07 a.m.]

Introduction

MR. BARNETT: I want to welcome you to this public meeting on the Prescription Drug User Fee Act, or PDUFA as we have come to call it. I am Mark Barnett with the FDA, and I will be serving as your moderator today.

As we all know, PDUFA authorizes the FDA to collect fees from manufacturers to help offset the cost of reviewing applications for new drugs and biologics, and you know that PDUFA is scheduled to expire September of 2002. Well before that happens, the FDA wants to take into account the views of its various stakeholders, that is, the people and the organizations that are going to be affected by this legislation. Of course, that includes manufacturers, health professionals, provide organizations, patients, and consumer groups, and, of course, that is what this meeting is all about.

Actually, this meeting is a continuation of a meeting we had last September, a similar meeting, and they have one thing in common, and that is that this is a listening meeting for the

FDA. We are here to hear your views about PDUFA.

The difference between last year's meeting and this one is that this year we are in a position to be a little more specific in presenting to you both the successes we have experienced with PDUFA and some of the new challenges that we are going to be facing in the future. So what we need from you is, in a sense, your perspective on PDUFA, how you think it has worked so far, what you would recommend for the future, your reactions to the program, how you think we should deal with some of the new challenges you are going to be hearing about, and whether PDUFA, in fact, has fulfilled your expectations for the legislation, and if not, why not.

We are going to elicit that information through a series of three panel sessions, each of them with several speakers. Each panel is going to include a range of perspectives. There will be the FDA, patients, consumer protection groups, health professionals, and provider organizations. In each of the panels, we are going to have the FDA speaker lead off and give some perspective on the agency's experience and assessment of the issues that are being faced by that panel, and then we will hear

from the various panel members.

Since we want to hear from as broad a spectrum of stakeholders as possible and not just the panelists, we are going to open the floor after each panel to an open discussion in which people from the audience can comment on what they heard during that panel, and the ground rule is that we will limit those comments and questions to what it was that the panel was discussion. If you have questions or comments on PDUFA not covered by the panels, we will leave time for that at the end.

When it comes to questions and comments from the audience, I wanted to mention that we cannot give you FDA positions on a given issue because, in fact, we are in the process of formulating those positions. So, if you ask us about that sort of thing, that should not be a great drawback because, in fact, this meeting is not for you to hear from us, but from us to hear from you.

As you know from the Federal Register notice, the panels were asked to consider three questions.

The first panel is going to consider public health outcome; that is, has PDUFA supported

the FDA's mission to protect and promote the public health and what in the program should be retained and changed as we think about the future.

The second panel is going to be talking about the post-market question; that is, should PDUFA permit user fee funds to be used to monitor the safety of a new drug or a biologic after it is approved.

The third panel is going to talk about funding; that is, how can the FDA ensure that PDUFA goals are being met during an era when the continues to be a funding shortfall, if the funding shortfall continues, what is to be done about it, how do we set review priorities, and if so, how do we do it, should there be flexibility in setting up user fees in order to cover whatever increased costs we encounter.

At the close of the last panel, in addition to hearing from the audience about the issues of that panel, we are going to also hear from a few individuals or organizations who have signed up in advance to make comments, and at that point, I will also open it to the floor for PDUFA questions not covered by the panel.

So we have a full program today, and in

order to make sure that everybody gets a chance to speak, including members of the audience, I am going to limit each of the speakers to 10 minutes. When there are 2 minutes to go, I will give an oral warning, and then we will cut it off at the 10-minute mark. I think everybody understands that in advance.

One of the things that everybody is reminded at a meeting like this is what is going to happen with the information. I mean, you are hearing it, but are you really listening, and are you going to do anything about, and the answer to that is yes. The FDA takes these meetings seriously, and we will, in fact, consider everything we hear today as we formulate a position.

In thinking about listening, I saw a cartoon in this week's New Yorker last night. A man is on a couch, a book in his lap, and the TV is on. His wife is sitting next to him, apparently trying to get his attention. In the caption, he says, "Of course, I am listening. I am in a state of heightened alert," so a sign of the times. But we are listening, and that is the message.

On that positive note, let me introduce

Dr. Linda Suydam, FDA's senior associate commissioner for Communications and Constituent Relations.

Dr. Suydam is going to give us a general overview of the PDUFA program, how it works, what it is supposed to accomplish, and what we have learned over the past year in implementing PDUFA as we prepare for reauthorization. She is going to give us an overview of the steps that the FDA is going to take between now and next September as Congress considers reauthorizing PDUFA.

Linda?

Opening

DR. SUYDAM: Thank you, Mark.

First of all, thank you and welcome to all of you. We really appreciate this opportunity to meet with people and hear about your views related to the Prescription Drug User Fee program.

Our consultation with stakeholders is, in fact, critical to the work that the FDA does. Even prior to the passage of FDAMA, we worked very hard to make sure that we heard from people across the spectrum of all of the groups that have actually an interest in FDA. It is central to our public health mission, and it is really essential to

meeting the goals of the agency.

FDA is no different than any other large organization in that getting results means that we need to keep thinking differently. We need to reexamine what we are doing, how we are doing it, and making sure that we are meeting all of the needs that we need to meet as an organization.

In our case, that means we have a lot of change in what we do. Products we regulate continue to become more complex. There are scientific advancements and uncertainties. Always, there is new knowledge, new expectations, and new standards. Obviously, there are altered national priorities, and I think after September 11th, it is very clear that our priorities have changed. All of a sudden, "bioterrorism," "counterterrorism," and "antiterrorism" have become words that the FDA needs to know and act on and be a part of, and the programs we have in that area did not exist in any great extent prior to September 11th.

PDUFA has evolved as well as the agency. Ten years ago, PDUFA was established, and the promise of it was to assure timeliness and to assure access of patients to new products.

Recently, the goal for PDUFA has been

stability, and 10 years from now, who knows what that goal will be? But we certainly how that, today, we can begin to capture what are some of the future needs for the PDUFA program.

As Mark said, we have 10 months remaining before the PDUFA program expires, and that is really scary to a lot of us in the agency because there is a lot to be done. As you can see, we had our first public meeting in September. We have had ongoing discussions with stakeholders. We had three smaller meetings in the last couple of months. We hope this will be our final public meeting today. We are looking at developing options and formulating positions. Obviously, we have to have draft legislative language. There have to be hearings in both the House and Senate. There needs to be markup and amendments, floor debates, and conference. We need to go through the entire legislative process, and the President needs to sign the bill by October 1st of 2002.

In prior years, we always had a carryover of money. This year, we will not, and so the program is in such precarious financial shape that we must have it reauthorized by October 1st of 2002.

Let me talk a little bit about what we heard at the public meeting in September of 2000. I think there was some general agreement that resources are key to the performance of this program, and we have proven that when we are well-resourced, we can do the job. We can do what is expected of us and meet the goals, but we also discovered that our non-PDUFA responsibilities are vital. We have had a difficult time in the last 10 years in budgets, and as a result, our non-PDUFA responsibilities are not as robust or healthy as they should be.

There were also divergent opinions expressed. Many people felt that the appropriation of the fees could, in fact, provide some conflict to the agency, could perhaps make us more biased than we would be, and that, in fact, Congress ought to be appropriating the dollars to fully fund the FDA.

There was also some debate on performance goals and what they meant, and those performance goals relate to accountability, predictability, and establishing goals. The problems with performance goals is sometimes they were met and perhaps that wasn't exactly what needed to be done. So we are

dealing with the performance goals as an issue.

Finally, should there be fees for other safety functions, for functions that are related to pre-market review, such as post-market surveillance and advertising?

As Mark said, today's meeting is going to focus on three topics.

Public health. Has PDUFA supported FDA's public health mission, and what are you ideas for changes or enhancements to that mission and to the program?

Post-market safety. Should fees be used to monitor safety after new drugs and biologics are approved? We want your thoughts on that.

Funding. How can FDA ensure that this program remains viable when funds are clearly short? What suggestions do you have for how we can maintain the viability of this program?

So, today, let's draw on our experiences with PDUFA I and II, and let's look at the new knowledge we have gained in science, medicine, and public health, and then work on the best way we can apply our resources to the common good. Together, as a group, we can help shape PDUFA III.

Public health outcomes have been

tremendous. The real question is can we keep that going. Post-market safety is more significant than it was in the last 10 years. Can it be addressed more directly? PDUFA is a financially fragile program. Can we add assurances for its financial viability in the future?

Thank you.

MR. BARNETT: Thank you, Linda.

Panel I - Public Health

MR. BARNETT: Let me now ask Panel I to come up and sit over here at the other table.

While they do that, let me give you a little housekeeping hint. There is a message board outside the room, over at the far end of the room, which you will see up on an easel. So you can look for messages up there.

[Pause.]

MR. BARNETT: If this is right, in addition to Dr. Zoon who is going to be our FDA representative, we have Travis Plunkett who is legislative director for the Consumer Federation of America, Susan Winckler who is director of Police and Legislation for the American Pharmaceutical Association, Amy Allina who is with the National Women's Health Network, and Richard Levinson who is

associate director for policy of the American Public Health Association.

So let's lead off with Dr. Zoon.

DR. ZOON: Good morning. It is a pleasure to have an opportunity to participate in this panel that is going to address the public health benefits and outcomes of PDUFA. This is obviously an area of great importance to all of us, and, certainly, the FDA is very much engaged in our assessments of this.

The PDUFA program, or the Prescription Drug User Fee program, was initiated with two primary goals in mind, one, to reduce the time required for FDA review of new drug and biological product applications and to, thereby, enable patients to have earlier access to therapies and vaccines. This program provided additive resources to the FDA, review staff, and systems, particularly information systems, that have allowed us to expedite reviews of important new products.

When we talked about the success of PDUFA, we often go on to talk about meeting our performance goals of the program and the resulting reductions in the average time to approval for new drugs and biologicals. Today, I would like to say

more about the drugs and biologics that we have been referring to because these are really the outcome that provide to the public the treatments and the vaccines to improve the health of our country.

These products touch patients across a wide spectrum of diseases, everything from cancer to infectious diseases. Some have helped to expand the options available to the medical community in treating patients that they serve. Others have provided therapies that have literally saved lives.

To date, 712 products have been approved under the Prescription Drug User Fee program. 198 are considered significant therapeutic advancements and have undergone priority review. They include 30 products for cancer, 37 products for AIDS, 29 products to fight infections, and 47 products to treat cardiovascular diseases. Ninety-five of the priority product approvals were used for new treatments. These are what we call often "new molecular entities" for conditions ranging from rheumatoid arthritis to sepsis.

With the priority review under the Prescription Drug User Fee Act, literally thousands of cancer patients have had earlier access to new

cancer treatments. This, in turn, extended many cancer patients' lives or improved the quality of their life.

One example is a new biologic for the treatment of breast cancer, Herceptin, which was approved by the FDA in less than 5 months. This drug too 18 months to be approved in Europe. There was an estimated 10,000 American patients with advanced breast cancer who received this new treatment during the time that FDA might have still been reviewing the application, had it not been for the improvements made with additional funds under PDUFA. This added about 2,300 years of life to the population who had access to this new treatment following its marketing approval in May of 1998. This is a significant impact on women with breast cancer.

Other life-saving therapies were also reviewed in less time than comparable drugs prior to PDUFA. Earlier access to a new drug for congestive heart failure is estimated to have prevented up to 2,800 deaths. With other new treatments, the earlier approval has helped thousands of patients to avoid significant sickness and hospitalization. For example, earlier access

to new treatment for osteoporosis is estimated to have prevented as many as 3,000 fractures among women who received this drug following its approval in the United States.

Many reviews of important products with pediatric indications have also benefitted from the resources provided from PDUFA. The faster review and earlier approval of a new vaccine, Prevnar, for life-threatening infections in children allowed earlier access of this vaccine and prevented an estimated 14,000 cases of serious infections in infants and young children.

Other important approvals of pediatric medicines include the first inhaled corticosteroid for children with asthma, a new treatment for newborn infants with respiratory failure, that helps increase the oxygen in blood and reduces the need for heart-lung bypass.

Recently, a new recombinant activated protein C has been approved for the reduction of mortality in patients with severe sepsis and who are at high risk of death, and a new breakthrough treatment for children with rheumatoid arthritis and a Pegylated Interferon for hepatitis C.

In summary, we think the additive

resources of PDUFA have played an important role in helping FDA achieve its goal of increasing patient access to safe and effective new medicines. It has made a very big difference in the lives of many patients.

With all of these many important parts of the program, the impact, I believe, has been very significant on public health. While we have been, and continue to be, supportive of this PDUFA program, one must look at the challenges, and some of those will be discussed later with respect to the post-marketing and the financial issues, but, all in all, this program has been an important part of our program and, we believe, has had a major public health benefit.

Looking at the FDA's program, probably one of our significant challenges has been during the time while we have had additive resources to PDUFA. In fact, until this year, we had not received cost-of-living for the agency to our base activities, and this has put a lot of stress on our non-PDUFA programs. And that raises a concern from a public health point of view that I think we need to address.

In closing, I would just like to say, we

look forward to the reauthorization of PDUFA, and we would very much like to hear your views on this program. We have two main questions for you today: one, in your view, has PDUFA supported FDA's mission to protect and to promote the public health; and, two, as we consider the potential shape of a PDUFA III, what should be retained or changed to enhance the program and to ensure a good public health outcome.

Thank you.

MR. BARNETT: Thank you.

I am going to call on the panelists in the same order they are on the agenda. So our next speaker will be Travis Plunkett from the Consumer Federation of America.

MR. PLUNKETT: Good morning. Thank you, Dr. Zoon, and thanks to the FDA for holding this public meeting.

My name is Travis Plunkett, and I am the legislative director with the Consumer Federation of America. CFA has worked with the Patient and Consumer Coalition regarding renewal of PDUFA in 1997 and will be working hard with the FDA and the Patient and Consumer Coalition on Capitol Hill regarding reauthorization next year.

I want to start by thanking the FDA for your consistent efforts over the last year to reach out to the public, to patients, to consumers, about reauthorization of PDUFA next year. You have done an excellent job, and we very much appreciate the opportunity to offer our comments.

To the first question, has PDUFA supported the FDA's mission to protect and promote the public health, well, if success is measured by the goals mandated in the '97 act, the answer is a resounding yes. The time for approval of new drugs declined from a median of slightly less than 2 years in 1992 to less than 1 year in 2000. It is now at about 15 months. A higher percentage of applications are now being approved as well.

Clearly, there are very important public health benefits--and Dr. Zoon has outlined some of them--to be gained from faster approval of certain new drugs. These include medications that treat serious and life-threatening conditions, drugs that provide relief for patients with illness or disability refractory to existing therapies, or drugs that are less toxic than currently available, but the success of drug review and approval should not be measured by speeding approval rates alone.

That is the major flaw of the '97 act.

The FDA's responsibility under law is obviously to ensure that new drugs and devices are safe and effective. If success is measured by a more balanced assessment where you weigh the advantages and the disadvantages of faster new drug approval, such as the negative public health effects of drugs that have harmed or killed Americans and have subsequently been withdrawn from the market, there is definitely cause for concern or at least further investigation. And if success is measured by the draining effect of PDUFA on the FDA's ability to achieve the rest of its public health mission, a fact that the FDA has openly acknowledged and we are going to hear a lot about today, then one can only deduce that PDUFA has not provided a net benefit to the public health.

Now, the flip side of some of the public health successes that Dr. Zoon pointed out is that there has been a going number of recalls and warnings related to newly approved drugs, and this has reinforced our concern that PDUFA, by providing user fees from a regulated industry to the regulator, represents a potential conflict of interest.

The agency has attempted to demonstrate, primarily talking about the withdrawal rate of drugs, that there is no relationship between faster approval times and more frequent recalls. Twelve prescription drugs have been pulled from the U.S. market in the last 4 years for safety reasons, by far the most such actions taken in any comparable period. Only three of these withdrawn drugs were approved before PDUFA took effect in 1993. The most recent withdrawal was the anti-cholesterol drug, Bakol, which is implicated in 31 deaths.

Now, according to a Pulitzer Prize-winning investigation by the Los Angeles Times, more than 22 million Americans took the drugs that were withdrawn prior to Bakol, and I would submit that this is the proper way to evaluate public health. It is not what the approval or disapproval rate is. It is how many people were affected, what they were exposed to, how dangerous the drugs were, and how important initially the drugs were for public health; that is, did they provide breakthrough therapies, did they provide life-saving potential, or were they "me, toos," were they just copies of drugs that are already in the market.

To the second question, what should be

retained or changed to enhance this program, we have a number of suggestions in the written comments that I have left for the FDA and should be available on the information table.

The best way to ensure the timely approval of safe drugs is to adequately fund the FDA from general revenues. Adherence to this principle would be the surest way to remove the worrisome potential for conflict of interest that arises when dedicated income streams flow to the regulator from the regulated.

Congress should also provide additional appropriations for the public health functions that are suffering, including post-marketing surveillance of drug safety, adverse-event reporting, generic drug approval, direct-to-consumer advertising, and food safety.

Secondly, regulated interests should not be allowed to inappropriately influence FDA functions through the use of new user fees. This is a topic of a lot of conversation right now.

If an unwillingness on Congress' part to appropriate adequate funds leads Congress to consider the expansion of new user fees, it is absolutely essential that there be a firewall

between these user fees and the dispersement of these user fees in the performance by the FDA of its mandated responsibilities.

At the State level, utility commissions and insurance departments often assess regulated businesses for the cost of oversight. Although conflicts of interest sometimes occur at these agencies, this approach gives the regulated industry far less control over the priorities of the agency in the manner in which success or failure is measured than a dedicated funding stream like PDUFA user fees.

Third, the PDUFA performance goals really need to be overhauled. There is absolutely nothing wrong with a Federal agency using performance goals as an internal management tool to achieve its public health goals, to hold its employees accountable to measurable standards, and to better serve the public. That is very good. However, the performance goals in PDUFA II have become far more than a management tool. They have given a regulated industry inappropriate and potentially dangerous control over the functions of the regulator.

I lay out in my written comments three

principles for overhauling these performance goals.

First, public health should be paramount. Medical officers and scientists, not one-size-fits-all deadlines that are rigidly interpreted, should determine the speed of new drug approval.

Secondly, the FDA has to be given meaningful flexibility to implement these performance goals. One way to do that is to write into the statute an override clause that says that any scientist or medical officer with the power to make this decision can slow down the approval process if public health concerns exist, without facing censure by the agency.

The third principle for overhauling performance goals should allow for greater differentiation within the standard and priority review categories. This would allow the agency to put the approval of drugs that are not breakthrough or life-saving therapies on the back burner if conditions warrant; for instance, if a national emergency arises, as we have now.

So, in conclusion, thank you very much, again, for reaching out to the public so well on this issue, and I look forward to working with all

of you to get a good statute on the books next year that protects the American people.

MR. BARNETT: Thank you.

Before we go on, let me ask whether the FDA panelists have a comment, a brief comment to make on Mr. Plunkett's remarks. Anyone?

DR. SUYDAM: No.

MR. BARNETT: All right. Let's go on, then, to Susan Winckler.

MS. WINCKLER: Good morning. As we noted, I am Susan Winckler. I am a pharmacist and an attorney with the American Pharmaceutical Association, which is a group founded in 1852 that represents pharmacists in all practice settings.

With that, our members, pharmacists, rely on a credible drug review process by the FDA, and this morning, as part of this panel, I will talk about whether the PDUFA program has supported the agency's mission to protect the public health and how PDUFA could be enhanced.

If we talk about a public health goal in one context, I think we can argue that PDUFA has helped meet that goal, and that is by promptly and efficiently reviewing clinical research. Through that new drug review process, the agency reviews

and, when appropriate, approves those new and beneficial therapies.

Prescription drugs can be a valuable tool in the prevention and management of chronic illness and disease when they are used correctly, and pharmacists certainly look to the FDA to ensure that new medications are only brought to the market upon completion of a comprehensive high-quality review.

Obviously, the revenue generated by the PDUFA program has allowed the agency to increase staffing levels and enhance the resources allocated to the application process for human drug and biologic products.

You have the statistics before you, and the assessment of those statistics is that the increased level of resources has clearly improved the time required for agency decision. However, it appears that we have a problem in that due to an increase in the number of new drug applications, the increasingly stringent annual review goals from PDUFA and funding levels that were lower than anticipated, it has been increasingly difficult for the agency to achieve a prompt review of new drugs.

It is evident that the amount of revenue

generated by PDUFA fees is not adequate for the agency to maintain its shortened review times and meet the increasingly stringent performance goals. Importantly, fees alone are not the answer and should not be perceived as the answer here. They are a very important portion, but we also have to look to sufficient appropriations, and I think that has been lost in some of the discussions with PDUFA and understanding that we need accompanying appropriations as well.

It is unacceptable that funding for a program as important as our drug review process was insufficient to keep pace with mandatory across-the-board pay increases. Additional appropriations must be provided to the agency to properly fund vital health programs.

While the PDUFA program has helped the agency meet its mission to promptly and efficiently review clinical applications, it appears that current levels of funding are not adequate for the FDA to sustain these gains and continue to approve drugs efficiently without compromising review quality and safety.

Speaking to the issue of how we could enhance PDUFA--because it is working at some point,

but we obviously need to deal with the appropriations question--there is also something beyond the new drug review process that should be addressed.

The agency's work does not end when the drug applications are approved. The agency is also responsible for monitoring drug performance after approval. The PDUFA program could be enhanced if it was expanded to fund other activities related to the overview of direct-to-consumer advertising and post-marketing surveillance. Both activities are crucial to the agency's mission to protect the public health by ensuring that drugs are safe and effective.

The PDUFA program does not currently provide funding for the review of direct-to-consumer advertising. Oversight of DTC activities should be added to the PDUFA-funded scope of work. The prevalence of DTC advertising is obvious to any of us watching television or reading magazines. A recent survey by the Kaiser Family Foundation found that 91 percent of all Americans had seen or heard a DTC advertisement for a prescription drug, but the benefits and potential risk of this expansion are not so readily

observable.

We hope that consumers are retaining adequate information from a DTC ad, including a clear understanding of the drugs' risks and benefits, but I do not believe we know that.

Are DTC ads increasing consumer and health professional dialogue? Has the explosion of DTC advertising yielded improvement in medication use, either through improved compliance or by stimulating consumers to seek medical care for untreated conditions? Or, by contrast, has the DTC explosion yielded an increase in the casualness with which our society treats medication, that there is a tablet to treat everything and all I must do is ask my doctor to get it? These questions must be answered.

The agency is pursuing an initiative to survey physician and patient attitudes toward DTC promotion of prescription drugs. APhA strongly recommends that the agency expand that survey beyond physicians to include pharmacists and other members of the health care team.

We appreciate the agency's efforts to examine the effects of DTC advertising on both the public and health care practitioners. An

assessment of the impact of DTC advertising on medication use, including prescribing and patient compliance, is essential. Adding such activity to PDUFA-funded activities would be helpful in making sure that when we have a drug that is reviewed and subsequently comes on the market, we know the impact of this activity known as direct-to-consumer advertising.

Post-market monitoring activities are also not funded by the PDUFA program. APhA supports the expansion of PDUFA-funded activity to include enhancements in post-marketing surveillance. Close monitoring of newly approved products is crucial to the agency's mission to protect the public health.

The reality is that some problems and benefits of products will not be discovered in pre-approval clinical trials. Medication use in real life is far different from the controlled environment of a clinical trial, with the concurrent use of other medications, over-the-counter products, and dietary supplements, as well as personal activities. These all impact how medications work.

Identifying the risks and benefits of medication use in real life will likely not benefit

from a slower review time. Only assessment of the extensive use of the medication in real life in the real market will identify those problems.

Rigorous post-marketing surveillance and early detection of potential problems is particularly important as the number of new molecular entities first introduced in the U.S. has increased substantially with the PDUFA activity.

According to the Tufts University Center for the Study of Drug Development, 80 percent of new molecular entities received FDA approval within their first year of introduction on the world market between 1996 and 1998, compared to only 43 percent in the previous 4-year period.

While the FDA approval of new molecular entities brings new drug therapies to the U.S. first, it also brings the agency an added responsibility because significant adverse events will likely be first detected here, if we are looking for them.

Providing the agency the resources to closely monitor newly approved drug products during the first few years the product is marketed could help identify potential problems before serious widespread patient harm occurs. We have heard

discussion of the withdrawal of products in the recent years, and most of that withdrawal had to do with the real use and whether the health care system was managing these products correctly, did we know enough about the products to make sure that they were used correctly and that the risk in them was minimized and the benefit maximized.

What we have here in our post-marketing surveillance and the withdrawal of those products is that patients lost access to a number of valuable medications because the health care system failed to appropriately manage risk. I think the FDA can help the health care system here, manage that identifiable risk and keep these products on the market, but we have to have more information in order to do that.

This reality creates an opportunity for pharmacists and the FDA to work together, focused on the profession's goal, to help patients make medications work. There are two problems in the important function of post-marketing surveillance at the agency.

First, FDA does not receive a sufficient number of adverse drug reports, far fewer than what we would expect compared to published reports

regarding the amount of morbidity and mortality associated with drug use. We should work with the agency to promote swift reporting of all adverse events to the FDA, but simply increasing reporting will not fix the situation.

The current reporting system is insufficient as a strategy to identify adverse effects and problems with appropriate prescribing and use of pharmaceuticals. FDA's current system for identifying unknown adverse effects of prescription drugs suffers from a lack of resources to analyze and respond to reports received by the agencies.

Use of PDUFA funds to improve this activity is vital to maintain the integrity of our drug review system, a system that relies on surveillance to identify, analyze, and communicate adverse events of products that are identified in real-life use.

Pharmacists can help with this, and we would like to work with the agency to use a promising mechanism to identify the problems, what happens once we get through the review process and bring these products to the market.

An additional component of post-marketing

surveillance would a new system for higher-risk prescription medications. Developing a standardized process to work with medicines or devices demanding special attention helps manage risks and optimize medication use. An enhanced risk management system should be developed through a cooperative effort among stakeholders, including patients, prescribers, manufacturers, and pharmacists. A system could use a standardized process to work with those high-risk medications.

Health professionals would know that a drug in the high-risk category bears special or unusual risks that require close monitoring, and a common system would allow pharmacists and prescribers to build these services into their practices.

I think the comment of the previous speaker in talking about, perhaps, a firewall between the fees and any expansion of activity may warrant more comment and may be the way to move forward with this. There certainly is a need for more activity to occur within the agency through additional appropriations and additional user fees, and discussion of those firewalls may be a way to move that forward.

I do appreciate the opportunity to present the views of the Nation's pharmacists, and let me express our support for the PDUFA program and its ability to support the FDA's mission to promote and protect the public health.

Managing the risk of the powerful technology we call medications is not, however, simply a function of the approval process. The risk must be managed when consumers use these products in real life. Pharmacists are essential to that management, and we look forward to continuing to work with the agency, consumers, and other health care professionals.

Thanks.

MR. BARNETT: Thank you.

Amy Allina.

MS. ALLINA: Thank you.

I am Amy Allina, the program director of the National Women's Health Network, and I would also like to start by thanking the FDA for inviting me to speak today and also for all that you have done over the last year to reach out to consumer advocates and hear our thoughts about the PDUFA program.

The network has spoken at past meetings

about PDUFA and has raised serious concerns about the program. Our greatest concerns about it relate to the ways in which we believe it has affected FDA's relationship to the drug companies the agency is responsible for regulating. We think that by establishing the user fee system and the PDUFA performance goals which were created in consultation with the industry, the Congress has undermined the agency's independence and the public's confidence in the quality of consumer protection that the FDA provides.

We are a member of two coalitions which share these concerns. One is the Patient and Consumer Coalition, previously mentioned, and also Prevention First, a coalition of independent health organizations.

This panel has been asked to address the question, has PDUFA supported FDA's mission to protect and promote public health. The network believes the answer to this question is no. In fact, we be believe that, on balance, PDUFA has detracted from FDA's ability to fulfill its mission to protect and promote public health.

While we do not dismiss the contribution made by faster approval of those drugs which have

represented genuine advances for patients and consumers, some of which were mentioned by Dr. Zoon, over the last several years we believe this contribution has been outweighed by the other effects of PDUFA.

Today, 4 years after the current PDUFA program was put in place, there is clear evidence that it has led to a reconfiguration of FDA's priorities and reallocation of its resources, to the detriment of the public health.

In the years since enactment of PDUFA, FDA's resources for functions outside of drug review have been reduced. This has impeded the agency's ability to meet its consumer protection responsibilities. The non-PDUFA programs which have been hurt include health fraud investigation, plant inspection, post-marketing surveillance of drug safety, oversight of drug advertising, among others.

As FDA has acknowledged in some of the previous meetings we have had, critical new drug safety work is not getting needed funding. FDA's non-PDUFA programs have absorbed inflationary costs and cuts to fund PDUFA, and FDA has been forced to reduce its work force and budget for programs other

than drug review to meet the requirements set by PDUFA.

In addition to the drain of financial resources resulting from the need to meet statutory spending requirements for drug review, the faster approval of drugs itself has increased the work burden on other parts of the agency without providing any more resources to meet the new demands. With more drugs being approved and more drugs being introduced first in the United States, as Susan noted, there are more drug safety problems to be managed after approval, but the parts of FDA responsible for managing post-approval drug safety have lost, not gained, staff and resources.

At the same time, other changes have taken place, which have also increased the workload of non-PDUFA programs. In the area of drug advertising, for example, spending on direct-to-consumer ads has skyrocketed in recent years, climbing from less than 800 million in 1996 to almost 2.5 billion in 2000. Yet, the FDA staff responsible for oversight of drug advertising and promotion has not been able to grow at anything like that pace.

As the Congress gets ready to consider

reauthorization of the PDUFA program, it is critical that lawmakers review the impact this program has had on the public health and recommit themselves to providing the FDA with adequate funds to allow the agency to fulfill its mission of protecting and promoting public health.

In addition to addressing the lack of adequate funds for the public health protection functions of the FDA, the network also believes there is a need for Congress to help the agency rebalance its priorities, which have been skewed inappropriately toward faster drug review by the performance goals established in PDUFA.

We believe it is time to consider establishing performance goals for the agency with respect to its functions protecting and promoting public health. Setting performance goals in, for example, the areas of Phase IV study completion and oversight of drug advertising would help ensure that these critical functions of the agency are not undercut by the need to meet drug review goals. Such public health goals could include a standard for the agency to have taken action against a percentage of companies that failed to conduct required post-approval safety studies or a standard

for the agency to review all direct-to-consumer advertisements for compliance and take action against violations within a set time period after the ad has been aired or published.

It is not even clear to us that the FDA could tell the public today how many of the post-approval safety studies that it has required as a condition of approval over the last 3 years have even been started.

All too often, once companies have received FDA's approval to market a drug, they fail to follow through with the Phase IV studies that FDA directs them to conduct, and we believe that if the agency had to meet a performance goal of taking action against companies that fail to conduct this required research, enforcement of approval conditions would improve.

With respect to review of direct-to-consumer advertisements, the agency reports that it is keeping up with timely review, but in at least one case, it took several months for the agency to respond to a complaint about an ad which was eventually found to violate required standards of accuracy and balance. This delay meant that by the time the company was notified

that FDA has found a problem with the advertisement, it had been running for several months and it had been seen by hundreds of thousands of consumers. Requiring that ads be reviewed within a specific time frame soon after being aired or published would improve accountability and encourage timely action in this area as well.

Similar performance goals for other consumer protection and public health promotion functions of the agency could be established. We do continue to be concerned about the inflexibility of the current drug review performance goals and also about the process by which they were established, but we would like to work with the FDA to create public health protection performance goals that have appropriate flexibility and input from consumers and public health experts.

I want to end by reiterating three points. First, Congress' decision to fund FDA's drug review through user fees has undercut the agency's autonomy from industry and undermined the agency's ability to fulfill its mission of protecting and promoting public health. Second, the fiscal demands of faster drug review and the establishment

of performance goals for that review have drained resources from critical public health functions of the agency and have inappropriately skewed FDA's priorities toward faster drug review at the expense of their ability to safeguard the public health.

Finally, in reauthorizing PDUFA, we would like to see Congress address these problems by recommitting itself to funding FDA at levels that make it possible for the agency to fulfill its public health protection functions and also by directing the agency to establish public health performance goals in consultation with public health experts and consumers, so that faster drug review no longer trumps all other functions of the agency.

Thank you.

MR. BARNETT: Thank you.

Richard Levinson.

MR. LEVINSON: Thank you.

My name is Richard Levinson. I am the associate executive director of the American Public Health Association. We are the world's largest association of public health professionals, 55,000 members and 76 different disciplines that make up the public health family.

As the last speaker on the panel, I am going to refer you to my published remarks for details. I am just going to highlight the agreements and disagreements that I have with not only what the previous panelists have said, but what has been said over the years about the PDUFA process.

First of all, I do congratulate the FDA for staying within the parameters of the PDUFA process. They have met the goals, almost without exception. They have brought to the market a number of very critical products for health and human safety. We know with the tremendous expansion in the biotech industry that many more products are on the market, and, hopefully, this expedited review process will also make them available to the public in a timely fashion.

We believe that they have given appropriate emphasis to drugs of high priority dealing with serious chronic illnesses and with untreatable illnesses, and we congratulate them also for that.

Like almost everybody else who has looked at this process, we have great concern, however, about the PDUFA process, even though we support its

renewal and continuance.

First of all, the standards. We think that the 2002 standards cannot be used as a floor or basis for the development of further standards. We think that they may already be too compressed, that they may be putting, despite additional staff and other resources--and I am just talking about pre-market review of drugs and biologicals that may already be putting too great a stress on the process of review in the FDA, and this may be--I am not saying it is, but may be related to the increased rate of drug recalls.

We are also concerned not only about the number of recalls, but the quality of some of them. We think that several drugs might not have been approved had there been additional leisure to go into greater depth about their possible side effects.

We think that the solution to forming better standards is certainly broadening the input of those who can comment on the drug review process. Public members, consumer members are absolutely essential, but they are necessary, not sufficient.

I think that there is a cadre of expertise

in the world independent of both the drug industry and the Government that can comment intelligently about the relationship between the volume of drug review process and its outcome, and we think that such people, either on a consultant basis or as a member of various review panels, should be permitted and encouraged to comment about future PDUFA regulations.

Second, we are concerned, as almost everybody else is, about what is covered by PDUFA, and you have heard a great deal and should hear a great deal more about post-marketing surveillance for adverse drug reactions, that it is certainly not adequate if there are 2 million hospitalizations every year for adverse drug reactions and 100,000 deaths. And that is probably a conservative figure.

We feel that this is very definitely, of course, an FDA function, but it should be much more adequately supported, and we think that user fees are an appropriate way to support this.

We are also very much concerned in this era of self-medication and self-management of health conditions, and we totally support this. We think this is a very good trend, but several

dangers creep in at inadequate regulation of over-the-counter drugs and of generics as well as direct-to-consumer advertising. You have read about some of the horrors of that process. It certainly needs to be regulated very vigorously.

We would also point out that we in the American Public Health Association are also concerned about other FDA functions which need to be made far more adequate. There are many of them. Of particular concern to us is their role in food safety. Certainly, the food supply, which is increasingly important, from overseas is a major open target for bioterrorists, and the FDA simply is not adequately monitoring imported foods. I will not go into that. That is not the purpose of this panel, but just to say that there are many other FDA functions that need additional function, and, hopefully, sources of this funding will be found.

I think that the idea of user fees to fund FDA functions is not inappropriate. I share everybody else's concern about inappropriate industry influence in this process and about conflict of interest. I believe that it has been fairly well prevented, and it can be prevented

further by appropriate legislation and by vigilance on the part of FDA staff.

I do not believe that the fear alone of improper influence should stop the use of user funds. I think the use of these user funds should be expanded.

Furthermore, I feel that the way in which they are used needs to be more flexible. You are going to hear more in other panels about the rigidities imposed with one-third from new products and one-third from establishments and one-third from existing products, and the '97 appropriation plus inflation as the basis for future appropriations. I think these things are inappropriate and artificial. The FDA should be given more leeway not only in terms of the use of the funds, but, also, of course, in the establishment and use of standards of performance.

I think that a great deal has been said, and I guess this gets into epistemology, if I understand the meaning of that term, about what is public health and what is not public health. What is said to be public health is a function such as post-marketing surveillance and direct-to-consumer advertising. On the other hand, what is said to be

not public health is the support of review of new drug applications and applications for new biologicals.

I am very much interested in philosophy, and epistemology, this distinction totally evades me. I think that everything that FDA does is part of public health. We consider it a public health agency. I am delighted to know that FDA also considers itself basically a public health agency, and I cannot make distinctions about what is and what is not public health. It is all public health.

Does this mean that Congress should support all of FDA's function? Yes, this would be very desirable. We in the real world know this will never happen. So the use of user fees from people who profit very grandly from the sale of drugs and other products is not an unreasonable way to support this function with adequate protections.

If the Congress is failing to support the rest of FDA functions--and I think there is adequate evidence that it is failing to do so--then it is the responsibility of people on this panel, people in the audience, people in the community who support the FDA function to lobby, or at least

advocate where you are not allowed to lobby, to Congress that the support should be more adequate, and the failure for FDA to achieve this support is as much a fault of ours as it is of anything that they might do.

I think this concludes my remarks, and as I said, I did want to highlight mostly my differences and support. My written comments will have more details about the APHA position.

MR. BARNETT: Thank you.

Now it is time to go to questions from the audience, or comments, rather. We would ask you to come up to the microphone in the middle, tell us who you are, where you are from, and then give us your comments. Remember, they are supposed to be focused on the subject of this particular panel which was public health. If you have other issues that you want talk about, we will save those for later.

DR. WOODCOCK: Mark, when you are ready, could I make a comment?

MR. BARNETT: Oh, yes. Go ahead.

DR. WOODCOCK: A number of the speakers on the panel alluded to the loss of support in other programs that FDA has, and there was a wide range

of comments, all the way to the foods program, the lack of robust program in those areas and what is the relationship to the user fee program.

I just want to correct any misconception people have that the user fee program caused this other problem. It may be that perhaps people felt the FDA was getting a lot of money from the user fee program and didn't require any money, but FDA lost $50 million every year in the cost of living for a decade, and our budget is only $1.2 billion or something like that.

Is that right, Linda?

DR. SUYDAM: Yes. It is $1.2 billion.

DR. WOODCOCK: So that is a very large percentage in real dollars that was lost.

At the same time, user fee money was added to the Prescription Drug User Fee program, but whether there is a cause-and-effect relationship, the loss in these programs is a problem we have had in funding, say to take a neutral topic, health fraud. Our health fraud program has shrunk dramatically. Parts of the device program, radiologic health, say, has shrunk dramatically. I don't think these are really a function that people were moved over to the user fee program. It was a

function of FDA had lost the support, the funds that we had available to actually have those people on board or fund those programs, just so that is clear.

Now, the user fee program may, in fact, remain more robust, the appropriated side, than some of the other programs, but by no means is it a cause-and-effect relationship. I just wanted to make that clear.

MR. BARNETT: Thanks.

Come on up to the mike if anyone has a comment.

FLOOR QUESTION: I am Reginald Ryan with Script World Pharmaceutical News.

Last year, a number of consumer groups actually opposed the reauthorization of PDUFA. I don't know whether Consumer Federation of America was one of them. I believe the Women's Health Network was. Is that still the position of the consumer groups, to your knowledge?

MR. PLUNKETT: We are going to oppose reauthorization in its current form.

We, just like everyone else on the panel, do acknowledge political reality. I spend a good part of my time on Capitol Hill. So, unless

President Bush decides very shortly to put me on the short list for those who might become commissioner, I probably won't have the power to impose my will on Congress or the administration. So we will deal with the political realities when we have to, but the concerns that the consumer and the patient groups have laid out are that in its current form we don't think it should be renewed.

MR. BARNETT: Yes.

FLOOR QUESTION: Good morning. My name is Chris Heeley, and I am the executive director for the Plasma Protein Therapeutics Association. PPTA represents the major products of plasma-derived and recombinant analog protein therapies to treat a number of rare disorders, including life-threatening conditions such as hemophilia and primary immune deficiency diseases, as well as many others.

Given the comments of the panel, I would just ask that as the day goes by, please don't forget the many, many rare disorders and rare conditions that are out there that stand to benefit directly from the benefits of PDUFA. Many of these patient groups already are subject to health surveillance by CDC, such as the hemophilia

community and others, and they really stand to benefit by making sure that there is timely review, a quick review of product and process improvement, safety improvements for the products that they take.

So, again, just to comment, please don't forget those many rare disorders that are out there that really have benefitted greatly from PDUFA.

Thanks.

FLOOR QUESTION: Good morning. I am Jay Lee from the National Center for Policy Research for Women and Families.

I just wanted to thank the panel for their comments today. I noticed that some of you had expressed some concerns about direct-to-consumer advertising, and I was just wondering whether there were any obstacles, legal or otherwise, that would prevent the FDA from requiring a review of these advertisements before they are released into the media.

MR. BARNETT: Comments from the panel on that?

MS. ALLINA: Well, probably, it would be better if FDA responded. They have certainly told us that they think there are obstacles to that.

DR. WOODCOCK: There are certain strictures that we have in our ability to regulate speech, basically, and we are able to look at these ads. For the broadcast ads, we have a voluntary program for the voluntary submission of direct-to-consumer broadcast ads before they are put on the air.

Ann Wine can actually explain. Ann Wine is in our Office of Chief Counsel, and she can explain the legal framework.

MS. WINE: As some of you, I am sure, are aware, FDA has been looking at issues related to direct-to-consumer advertising, both the policy issues and the legal issues, for many years, and continues to do so. I think there could be, certainly, an entire day's worth of discussion about both the policy and legal issues related to direct-to-consumer advertising.

I think what people are focusing on today is what is the relationship between whatever review of direct-to-consumer advertising FDA does and the user fee program and whatever the best approach is to whatever, either voluntary or required, actions are taken to make sure that the advertising is both appropriate, and I think what the consumer groups

are saying is to make those ads beneficial and not detrimental to the public health.

How to make sure that there is appropriate funding for this program is the question that is being addressed today, and I am not just trying to completely avoid the issue here. What I am saying is these are complicated issues from a policy and legal perspective, and maybe there is agreement that there needs to be an adequate program in place. If there is agreement on that point, then the question is how do you fund it, and should user fees help to fund that program.

I think at least some of the panelists have been clear on their position. If other people have different positions on that point, I think that the agency folks would certainly like to hear.

MR. BARNETT: Thanks.

Any comments? Yes.

MS. ALLINA: I wanted to just respond to Dr. Woodcock's earlier clarification about the relationship of reduction of other areas outside of drug review. Really, I am reiterating a point that I made in my comments, but I wanted to clarify myself that I was quoting from a presentation done by the FDA at our previous meeting in which they

said that FDA's non-PDUFA programs have absorbed inflationary costs and cuts to fund PDUFA.

MS. MULLIN: I am Theresa Mullin, and let me say from the planning shop perspective that that may be de facto what has happened, but I think it is different. That is not the same as saying this is the fault of the PDUFA program.

What it reflects is an interaction of what might be viewed as a reasonable provision under other circumstances, other budgetary circumstances of spending only an inflation-adjusted amount from the prior year if you don't make any assumptions about what the overall appropriation is going to be, but what we have experienced is very limited growth of our appropriation overall, and, certainly, in the Center for Drugs, actually flat to declining appropriations over the past 5 years. You put that together with earmarks of that money for other things, and then you put in this otherwise what appears to be reasonable inflation-adjusted spending from appropriations on PDUFA. The intersection of those things is what I think we are dealing with.

I think it is helpful to keep those concepts separate. I think many of you have talked

about those as sort of separate things.

DR. WOODCOCK: Amy, I apologize because I recognize that, but it is a little more complicated than simply that PDUFA sucked up all the money. The fact is we didn't get money, and we had to keep our programs going. So I am completely neutral about where the money comes from in the sense of if we are going to operate a program, it has to be funded. That is a basic business principle is that you got to have resources, and so I just think it is easy to say, well, the PDUFA program caused all that, but by no means is that the story is what I was saying.

MR. PLUNKETT: I am afraid this might be an argument over a distinction without a real difference.

DR. WOODCOCK: I don't think we are arguing. We are just trying to clarify what happened.

MR. PLUNKETT: A discussion.

DR. WOODCOCK: Yes.

MR. PLUNKETT: I don't think any of the folks who have raised concerns have not acknowledged that the backdrop to all of this is that Congress has not adequately funded the agency,

and then if you have these mandated cost-of-living adjustments, then that drains a greater and greater proportion of the agency's resources.

MS. ALLINA: And also that it is an interaction as well between appropriations and performance goals. As you said, if you have to keep your programs operating and you have performance goals for faster drug review and not for anything else, that is going to skew the decisions.

MR. BARNETT: Anyone else in the audience want to come up and join in?

[No response.]

MR. BARNETT: If that is the case, I think it is time for our break. My watch says 15 after. Let's be back at 25 after.

[Recess taken at 10:17 until 10:34 a.m.]

Panel II - Post Market

MR. BARNETT: Can I ask the second panel to convene up here on the platform.

[Pause.]

MR. BARNETT: Lets's get underway, then, with our second panel, and the focus here, remember, is post-market issues as they relate to PDUFA.

Our FDA speaker is Dr. Janet Woodcock, who is director of the Center for Drug Evaluation and Research.

Dr. Woodcock?

DR. WOODCOCK: Thank you.

I am just going to talk about the post-marketing program and what it is and what it can and can't do as a basis for, then, our panelists' comments.

Post-marketing surveillance is required, as Susan Winckler already alluded to in the prior panel, because when we approve a drug or a vaccine, we don't know everything about it. I would really like to reiterate that it isn't a function of the fact that we didn't spend time reviewing it. It is that we really haven't seen everything that is going to happen with a drug or biologic in the clinical trials, and unexpected findings often emerge after widespread use. It is kind of expected that unexpected findings will emerge because this routinely happens.

Why is this? Well, there are rare side effects that you just don't see unless a lot of people are exposed to the drug or the biologic.

Once the drug or biologic is approved, it

is going to be used in different populations or different circumstances than actually it was when the drug was studied in the clinical trials, and this is simply a reality we have to face. We don't see every kind of circumstance in the clinical trials. We don't see the off-label use that is often seen.

The other thing that happens is that certain interactions occur. As Susan said very eloquently, it is drugs, dietary supplements, other substances that people may be taking over the counter. We can't predict every kind of interaction that might occur. So, in other words, we learn things, good and bad things about drugs after they are approved, and so that knowledge needs to be captured and disseminated to the public and health professionals to maintain the risk-benefit ratio of drugs.

Unfortunately, our drug and biologic surveillance system is severely challenged, but this is not new news. I have in my files a report to Senator Kennedy in 1980--and by my count, that is almost 25 years ago--that called for a reform of the system. It called for increasing the resources. It called for creation of new

structures and so forth put into place, and, unfortunately, none of that happened, and the system that we are talking about today is the same kind of system that was the subject of that report in 1980.

There have been numerous studies in the medical literature and the public health literature since that time and editorials calling for improved surveillance, and, yet, this hasn't changed very much.

There have also been called for additional oversight even. Some commentators, as many of you probably know, become so frustrated they have asked for a new agency to be formed to oversee drug safety problems.

In addition, there has been a growth actually of the reports that we have to deal with, and I will get into that a little bit later.

What kind of system do we have? What are we talking about here? Well, the foundation of our surveillance for FDA for drug and biologics, we call spontaneous reports, voluntary reporting by health professionals.

If they report to a manufacturer, then the manufacturer must report to the FDA. That is

mandatory. The MedWatch program is the voluntary piece where health professionals can report directly to the FDA. That is what we have.

These reports pour into the agency, but they are strictly voluntary in the case of the health care system, and then we have to make sense of them at our end.

We made a major effort in the mid to late 1990's to modernize--actually have a database, and we have achieved that. We call that our AERS system, our adverse-event reporting system. It is a computer database and electronic reporting system that keeps all of this information there and allows our safety evaluators to analyze the database. That was a successful innovation that is continuing, but that doesn't create a new system. That is simply a database to support the spontaneous reporting system in a modern fashion.

When we get all of these reports, though, we may not know what to make of them. For example, say a report is people have been in motor vehicle accidents. Well, we don't know. Is it because the drug is impairing driving performance, or is that because people happen--every day, on my way to work, I see somebody in a motor vehicle accident.

So we have to do further analysis, and the way we do that is try to work with linked databases in the health care system and get other data that can allow us to make sense of we are getting spontaneously reported to us.

Unfortunately, the funding for that has had to be cut over the years. It is severely limited, and this is truly a shame because now, with managed care and so forth, there are lots of these linked databases out there, and there are lots of way to discover what is happening out there in the real world to people as they take these drugs.

We also lack enough staff, safety evaluators, epidemiologists, and other scientific staff that are needed to analyze this data pouring in and making sense of it .

In addition, since 1980, of course, our system has become more stressed. There have been increases in the number of drugs and biologics approved, and I call this the gift that keeps on giving because, when we approve a drug or a biologic, we don't get just the reports next year. We continue to get the reports all through the life cycle of the drug, and then it may go on generic

and it may raise new issues and so forth.

In addition, as already been alluded to by another panelists, the user fee program has probably doubled our rate of being first in the world. Why is that important? Well, it is important because when you are first no other population has been exposed before. As I earlier told you, we find out these things when large numbers of people are exposed out in the real world.

Back in the '80s when drugs were first approved in Europe or other countries, those populations would be exposed. We look back in our files and we can see drugs where the Europeans had a problem with that drug and we were still reviewing it in our long review process, and it was pulled off the application before it even got on the U.S. market.

You heard from Kathy about the benefits of getting many of these drugs to our patients earlier. On the other hand, we have to recognize that that brings a cost in terms of additional risk from uncertainty about certain side effects.

In addition, there has been a dramatic increase since 1980, if you use that as the bench

mark, in drug utilization, and that has stressed our system.

Let me just show you a couple slides of numbers. This just shows from '92 to 2000, the number of dispensed prescriptions. This is just the outpatient world, 3 billion. We are up to 3 billion prescriptions in 2000.

This is the number of reports of different kinds that are coming into this system I have described to you, this adverse-event reporting system. The yellow bars are the serious unexpected adverse events. They are serious. In other words, people do report their headaches and upset stomachs to us from drugs, but what we are really concerned about here from a public health impact is the serious ones. You can see we get almost 100,000 of those in '00. Unexpected means that health care professional, that manufacturer didn't think that was on the label or thought it was of greater severity than was described. These are things we have to jump on. That is 100,000.

In addition, you can see the overall reports are very high, and, yet, the direct reports, the purple boxes, that we get directly from the health care professionals is very limited.

We know we could increase that dramatically by promoting the system, but I think we only have three people working on the MedWatch program.

In addition, I think another thing that we forget about, because you tend not to take the long view here, is that public expectations have really changed for the FDA and our programs. In the past, when there were not so many drugs, the risk management was really felt to be by the medical community, the health care provider would know everything about the drug, decide if it is right for that patient, have access to all of the information, and apply it in the prescribing situation, but now there are too many drugs and the health care system is too stressed. Really, the public and Congress expect--and we ourselves at FDA expect ourselves to take an active role, to make sure that health provider is informed, make sure that information is out there before people who need it. So that has changed and also stressed our system because it is very difficult in the current environment for us to do this.

In addition, another stressor or change is the recognition, which we have recognized for a long time, of medical errors. Pharmaceuticals are

prominent in medical errors. The Institute of Medicine thought maybe there are 50- to 100,000 hospital-based fatalities per year due to errors. The data show that medications are involved in about a quarter of these at least.

We have a small post-marketing program at FDA aimed at preventing errors in the use of products. Some of this is just structural, is the product packaged right, is it labeled in a way that won't be mixed up with another medication during an emergency situation or on a prescription, but others is the whole risk management, do the providers have the risk information they need to make logical decisions for patients about risk.

We have instituted formal risk management programs for some products in the last 5 years where it was becoming clear from the reports coming in that prescribers were not logically taking this into account. They were giving teratogens to women of child-bearing age, for example, without doing a pregnancy test.

MR. BARNETT: Two more minutes.

DR. WOODCOCK: I'm sorry. I'm done.

How does this relate to the user fee program?

MR. BARNETT: You are done with that slide, you mean.

[Laughter.]

DR. WOODCOCK: How does this relate to the user fee program, though? I have just sort of laid out what our post-marketing program is and what the status of it is right now. Well, as I already said, we think the rapid pre-market review process has to be predicated on the fact that there is a robust post-marketing surveillance. We cannot just have one side of the program and not have the other side of the program.

"U.S. first in the world" means our population is placed at greater risk because we are going to discover these new adverse events in our population. The speed then becomes important. We want to discover them fast and get that information out. So we limit the number of people who might be exposed to those.

Effective drugs, as was already alluded to by the past panel, may be removed from the market if the risk management of them is not done properly. So it isn't that useful to speed the availability of drugs if then they become unavailable.

Public confidence, as you have already heard, in the drug regulatory system must be maintained, and part of that is the confidence that there is a robust safety net for adverse events.

So this relates to the questions that we have for this panel, which are supposed to be up here, but I think you have them.

Thank you.

MR. BARNETT: Thanks very much.

Let me pause now to introduce the non-FDA members of the panel, and, again, I will ask each person to just raise their hand so the folks out there know who I am talking about.

Robert Griffin is associate medical director for Blue Cross/Blue Shield of Vermont. Diana Zuckerman is president of the National Center for Policy Research for Women and Families. Jeff Bloom is with Patient and Consumer Coalition. Judy Cahill is executive director of the Academy of Managed Care Pharmacy.

Again, I will call on the speakers in the same order that they appear on the agenda. So we will start with Dr. Griffin, please.

DR. GRIFFIN: Thank you.

Good morning. I am Dr. Bob Griffin. As

noted, I am from the Vermont health plan for Blue Cross/Blue Shield. However, actually, today I am representing the National Blue Cross/Blue Shield Association which represents the 44 independent locally owned Blue Cross/Blue Shield plans that provide coverage to 81.5 million members. That is approximately one in four Americans.

Blue Cross/Blue Shield plans have extensive experience in providing prescription drug coverage to American consumers through a variety of our products.

I would like to thank you for the opportunity to appear before the Food and Drug Administration at today's public meeting on the PDUFA act.

I am here to address the specific question posed in the Federal Register notice for today's meeting, and that is, should PDUFA allow the use of the user fee funding to monitor safety after new drug or biologic approval. Our short answer is yes, we certainly think so, but let me summarize the association's recommendations on PDUFA.

We believe that an integral part of delivering new drug therapies to physicians and consumers is assuring consumer safety after the

drug has penetrated the market. By funding only the pre-market review of new drugs, PDUFA speeds access to new therapies, but that does not provide the FDA with the necessary resources to conduct critical post-market surveillance activities that keep patients safe.

In addition, the association believes that the flow of new drugs to market must be accompanied by health outcomes information that allows consumers to make value-driven decisions.

We also support continued increases in Federal appropriations for the FDA to provide resources for agency programs that impact public health.

To ensure consumer safety at each stage of the drug product life cycle, we specifically recommend expanding PDUFA's definition of "user fee-funded activities" to include post-marketing surveillance of adverse events and the monitoring of the risk and benefit information and the direct-to-consumer, or DTC, advertising, supporting FDA initiatives to require manufacturers to provide information that allows evaluation of the benefits, costs, and risks of new drugs compared to the benefits, costs, and risks of drugs already on the

market, and increasing Federal appropriations for the FDA to provide resources for agency programs that impact public health.

Thanks to PDUFA, more new drugs are coming to the market faster than ever. However, resources for important activities that ensure these new products are safe and effective for consumers have not kept pace with resources for drug review. PDUFA provides funding only for tasks that lead up to a decision on whether to approve or deny a new drug application. Post-marketing regulatory activities that are critical for all new drugs, such as tracking and responding to reports of adverse drug reactions and monitoring drugs advertisements for compliance with agency regulations, are not covered by user fees. Thus, these vital consumer safety responsibilities must be paid for out of congressional appropriations and may be at risk if the volume of new drug requests siphons funds from other FDA activities and Congress fails to sustain the increased funding granted this year.

Last week, Congress and the President signed a record budget for the FDA for fiscal year 2002. This represents the first increase in

appropriations for drug reviews since 1992. The Blue Cross/Blue Shield association applauds Congress and the administration for their recognition of the agency's role in protecting public health. We are encouraged that appropriations measures also enables the agency to meet the statutory triggers for collection and use of PDUFA fees without diverting resources from other key agency programs.

However, as noted, there is ongoing need for funding for critical agency responsibilities. Despite the welcome infusion of appropriated money fro fiscal year 2002, Congress must commit to long-term funding for the FDA.

I would like to discuss our specific recommendations. First, we recommend that Congress amend PDUFA to include post-marketing monitoring of adverse drug events as a user fee-funded activity. This will give FDA the resources to speed consumer access to new therapies and conduct critical post-market surveillance that keeps patients safe.

Not all of the drug's potential side effects and interactions can be known at the time of market entry. Indeed, these events manifest themselves gradually as the drug is accepted into

clinical practice and is used by an expanding patient population for the first time.

Currently, the FDA relies on voluntary reporting of drug adverse events by consumers and health care professionals. As more and more new products enter the market under PDUFA, the volume of adverse event reports has grown substantially.

According to CDER 2000, the FDA received 246,000 reports of drug-related adverse events in calendar year 2002. The GAO in its report, "Major Management Challenges and Program Risks," released in January 2001, stated the FDA estimates, however, that it receives reports for only 1 percent to 10 percent of the serious adverse events.

As the FDA recognized in announcing this meeting the agency lacks sufficient resources to adequately monitor reports of adverse events and conduct timely safety interventions. The FDA also noted that the current system for detecting adverse drug and biologic events does not provide sufficient data on the actual incidence of problems.

When Blue Cross/Blue Shield association last testified on this issue before the FDA in September 2000, we cited the withdrawal of several

drugs as examples of the need for PDUFA funding for post-market surveillance. Since that time, two more drugs have been withdrawn from the market for safety reasons, Lotronex for irritable bowel syndrome and Bakol, a cholesterol-lowering drug. This further illustrates our point.

We believe Congress should provide specific funds and require FDA to develop and implement a comprehensive protocol to monitor adverse reactions related to new drugs entering the market. The association supports a proactive role for the FDA in collecting adverse event data. We understand that the FDA's 2002 budget request approved last week included $10 billion to monitor marketed products and safeguard patients against adverse events associated with the use of drugs, biologics, and medical devices. However, there is ongoing need for funding of this critical task.

Congress must commit to long-term funding for post-market surveillance of drugs. This cannot just be a one-time event.

The association also believes that consumers faced with a barrage of advertisements for new drugs entering the market must receive clear and understandable information about the

benefits and risks. As such, we recommend that Congress also amend PDUFA to include monitoring of DTC advertising as a user fee-funded activity. We further recommend that Congress require the FDA to establish criteria for the level and type of information that consumers without a medical background need to make informed choices concerning advertised drugs. As more new drugs reach the market faster under PDUFA, they are marketed directly to consumers.

Recent surveys raised questions about the effectiveness of DTC advertising in communicating the important information about drugs. A survey released last month by the Kaiser Family Foundation found that nearly a third of adults have talked to their doctors about a drug they saw advertised, and 44 percent of those who talked to the doctor received a prescription for the drug that they asked about. This means that one in eight Americans have received a specific prescription in response to seeing a drug ad.

However, when asked for a self-assessment of how much they learned from viewing a specific ad, most responded, about 70 percent, said they had learned little or nothing more about their health

condition, and a majority, 59 percent, said they knew littler or nothing more about the drug.

In addition, according to the 1998 Scott Levin study, most physicians are also skeptical of the quality and the objectivity of the information presented in the ads. By expanding the definition of user fee-funded activities to include this critical regulatory requirement, Congress will help ensure that consumers have more complete, accurate, and understandable information about the risks and benefits associated with prescription drugs.

Our second recommendation that the FDA review PDUFA's role in ensuring that the rapid flow of new drugs to market is accompanied by information that allows consumers, physicians, and health plans to make value-driven prescription drug decisions. Specifically, Blue Cross/Blue Shield association recommends that the FDA support initiatives to require manufacturers to provide information that allows a comparison of benefits, costs, and risks of new drugs that replace existing therapies.

Some of the drugs that reach the market faster under PDUFA will truly be breakthrough processes, offering treatments where no effective

treatment currently exists. These drugs are likely to be the treatment of choice by physicians and their patients and will bring valuable benefits to consumers.

Other newly introduced drugs will simply substitute newer, more expensive drug treatments for existing cost-effective agents. Because the marketplace is becoming more and more competitive with many therapeutic classes, relative cost-effectiveness information is becoming more important.

For example, consumers, clinicians, Government and private payers need more information about the relative value of various asthma treatments in terms of symptom-free days, decrease in work loss, and any decrease in the emergency room use or inpatient services. Quality-of-life data is also an important determinant of value. By supporting initiatives to require manufacturers to provide information that allows a comparison of benefits, costs, and risks of new drugs that replace existing therapies, the FDA will help to ensure that Americans have continued access to breakthrough medical treatments and the right information to make informed choices about their

own medical treatment.

Given the critical consumer safety functions the FDA performs with respect to new drugs and under many other important agency programs, sustained increased congressional appropriations are necessary. The association's final recommendation calls on Congress to match the 2002 fiscal year appropriations level each year going forward adjusted for inflation.

We look forward to working with the agency, the pharmaceutical industry, and other stakeholders on this initiative to achieve the goal of a fully funded FDA that has the resources to carry out its public health and safety mission.

In conclusion, the Blue Cross/Blue Shield association is very concerned that accelerated drug reviews under PDUFA have not in the past been accompanied by comparable funding for consumer safety initiatives. We believe that as user fees speed new therapies to consumers, there is a comparable need to ensure that these drugs are safe and effective and the consumers receive complete and accurate information about the risks and benefits associated with their use.

Finally, we applaud the FDA for addressing

this critical health care issue, and we support the agency in any of these endeavors.

Thank you.

MR. BARNETT: Thank you, Dr. Griffin.

Diana Zuckerman?

DR. ZUCKERMAN: Thank you.

I am Dr. Diana Zuckerman. I am president of the National Center for Policy Research for Women and Families, and the theme of my remarks is going to be we need to know more. I, first of all, want to thank you all for the opportunity to speak today and for holding this very important meeting.

I think everybody in this room knows that during the last few years, there have been several very widely used drugs that were removed from the market after they had been approved, and it is abundantly clear that the approval of a drug or a device that is based on relatively short-term information may not tell the entire story about the safety of that medical product.

As Dr. Woodcock said--and I agree completely--it is not necessarily that there is anything wrong with the approval process. It is that the way the approval process is, you are only going to get pretty much short-term information.

Under the current PDUFA, the user fees are not allocated for monitoring the safety of medical products that have been approved, as we all know, and so, as a result, as everyone has already said, there are very limited resources for post-market surveillance. This is a dangerous situation that really must change.

The current situation is a recipe for disaster as more and more drugs are sold to more and more people soon after approval. Here is the recipe.

I must say, my family would be surprised I even know what a recipe is.

[Laughter.]

DR. ZUCKERMAN: Here is the recipe. Number one, approve drugs more quickly.

Number two, approve medical products that have known serious complications and adverse reactions saying that it is up to the physician and the patients to weigh the risks and benefits, but then not have the authority or the resources to ensure that physicians and patients have the information they need to objectively review that information.

Number three, spend billions of dollars on

direct-to-consumer advertising and promotions to physicians, thus, ensuring that very large numbers of consumers will be taking these drugs as they are made available and when they are still very newly available.

Number four, rely on the manufacturers to do the post-market studies and spend very little Federal resources to ensure that products are studied carefully after they have been approved.

Number five, spend very little money or resources to study the adverse reaction reports that are made or even to make sure that the reporting system is working appropriately.

As you can see for these five ingredients, we can share the blame of who is doing what. I am certainly not blaming the FDA and I am not blaming any particular entity. If Congress is not giving enough money, is not providing the ability for the FDA to have the resources, then certain efforts are going to be inadequate. Of course, if the law also ties the FDA's hands in terms of what they can and cannot do, then the law needs to be changed.

As somebody who worked in Congress for 10 years, when I talk about PDUFA and how it needs to be changed, I don't necessarily think of what it

looks like right now and how to tinker with it, but how to make some rather more dramatic changes.

But we have got the five ingredients. Quick approval, approving of medical products that are known to have adverse reactions, but relying on the physicians and the patients to figure out whether the benefits outweigh the risks, direct-to-consumer advertising and billions of dollars for advertising to physicians as well, relying on the manufacturers for a lot of these post-market studies, and having few resources to review the reports that come in as we saw in the slides.

So we stir this altogether, and the results are clear. The results are going to be that some products are going to be on the market for an extended period of time after people are starting to have rather serious adverse reactions, and, of course, we all know that there will always be some adverse reactions to any product. We are not naive about that, but when you have millions of people or hundreds of thousands of people or even tens of thousands of people taking drugs, you are going to see some adverse reactions that obviously weren't apparent when the drug was approved, but we

still need to know about that as soon as possible. Under the current system, we are not finding out about it as soon as possible.

Because of PDUFA, there are fewer resources available to the FDA to conduct or monitor post-market surveillance, and I won't get into that distinction without a difference of how much is Congress' fault for not providing more direct appropriations for the FDA and how much is a law that requires user fees to be used for specific activities and not to be used for others.

As bad as the situation is for drugs and biologics, consumers with implanted medical devices are even more vulnerable, and this is part of an even larger problem because PDUFA does not refer to and does not include medical devices. Yet, post-market surveillance, particularly for implanted medical devices, seems obviously, extremely important. If you have an implant in your body, wouldn't you like to know what the long-term impact is going to be?

I am going to provide four brief examples of the need for better post-market surveillance. Number one is the well-known example of Fen-phen, a widely used diet pill, used by thousands of people,

mostly women, some of whom died or experienced permanent health problems as a result. Fen-phen were two drugs that were separately approved, but were not approved as a combination use.

The risks were discovered by health professionals who happened to see several women who had these very unusual health problems, rare health problems, who they knew they had also seen in their diet program taking diet pills. If those women had gotten Fen-phen from the Internet or from some other medical facility--I mean, this was just luck that the women who were seen in one part of this medical facility for their diet pills were also seen for their other problems. So the health professionals there happen to notice it. If it hadn't been for that, it would have been even more years before this link had been discovered.

Number-two example, I would like to use a medical-device example of jaw implants. Jaw implants are a permanent device used to treat TMJ disorders, and they were fairly recently approved by the FDA, despite very high patient attrition rate in the studies. So studies were done that were supposed to be long-term studies, but most of the people in the studies did not have any data

collected after the first month or so.

In that particular situation, the FDA's advisory committee made it clear that careful post-market surveillance was absolutely essential, but there is no evidence that that has been done.

In the meantime, and even before the approval of these devices which were grandfathered devices, some patients have reported debilitating pain, permanent damage to the jaw and the skull, including holes in their skull, and other serious health problems caused by the implants.

It is widely agreed among health professionals that terrible adverse reactions can occur with these jaw implants, but because of the lack of research, nobody knows how often that happens and whether, in fact, the benefits of these implants do outweigh the risks.

My third example, briefly, will be saline breast implants which were approved by the FDA last year, despite a 3-year complication rate of more than 70 percent--more than 70 percent among mastectomy patients who had saline implants for reconstruction. In fact, the complication rate was so high that there were members of the FDA advisory committee who questioned whether it could actually

be true, and they started thinking, well, what did they mean by pain, did they mean unrelenting pain or did they mean just the kind of normal pain that you would have after surgery.

They also wondered whether the multiple surgeries that so many of the patients were reporting were due to problems with the implants or, again, part of the regular reconstruction process where a nipple reconstruction is done after implants are inserted, some months later.

Again, the advisory committee made it clear that careful post-market surveillance was absolutely essential, but, again, that hasn't been done. In fact, the FDA has received more than 65,000 adverse reaction reports for saline breast implants and more than 127,000 adverse reaction reports for silicone gel implants, but all of these reports have not been comprehensively evaluated yet.

Meanwhile, a study by the National Cancer Institute suggested that there are potentially long-term risks of implants related to various cancers.

So, again, we don't yet know because the NCI reports aren't studies of the implants that are

currently on the market. They are previously made implants. So we need studies to find out what is going on with the implants that were just approved.

Then I will just very briefly mention cholesterol-lowering drugs, this is something that is close to my particular heart because my husband is on them. Now, my husband started feeling not quite right after he had been taking these drugs for a while, and he is a physician. Those of you who are a physician know that that means that he either will do nothing at all about it or thinks he knows all about it even when he doesn't, but in this particular case, he knew that something wasn't quite right.

So he went to his doctor who was not really able to tell him anything other than what he already knew, which was that there are some studies suggesting some potential problems.

Then there was the question of what are the risks of cholesterol-lowering drugs, obviously clear benefits, but what are the risks and do the risks outweigh the benefits, and he was left in a situation of not really knowing and just assuming that, of course, the FDA would be doing post-market surveillance of these drugs. But I think it is a

really good example of a physician who even did manage to go see another physician for advice, and between the two of them, they still didn't really have the information they needed to make a reasonable decision of what is best.

So here is just four examples of how drugs and devices can be approved when the long-term safety is not clear and how our current system doesn't enable the FDA to have the resources it needs to do the post-market surveillance that is so essential.

We are currently mostly relying on manufacturers to do this work, and we know from experience that a manufacturer might be reluctant to admit that they are selling a product that could potentially cause serious health problems, and that is why we have regulatory agencies.

This is a dangerous situation for consumers across the country, and a recent GAO report tells us that the health products that have been taken off the market most recently were disproportionately used by women and disproportionately caused harm to women.

The FDA clearly needs more money and staff to do post-market surveillance and related

activities, and whether that money comes from PDUFA or whether that money comes from Congress, it has to come from somewhere and it has to be stable over time, but, in addition, I think it is very clear that the FDA needs more regulatory muscle in addition to more resources to enable them to regulate these medical products that are already approved. And I would say especially implanted devices and drugs that are taken for chronic health conditions.

Potential strategies. Changing the system of post-market surveillance with a stronger regulatory role for the FDA, increasing user fees and including the cost of comprehensive post-market surveillance in those user fees, requiring user fees for medical devices pre- and post-market. I didn't have on my list, but I very much agree with the idea of direct-to-consumer advertising and better regulation of those ads as part of what is necessary for this process. Changing the formula used in the allocation of Federal funds for various FDA regulatory and scientific activities in PDUFA, if it is going to have a formula, that needs to be changed, dramatically increasing the amount of Federal funds and staff available for post-market

surveillance of drugs and devices and, of course, just some combination of all of these things.

So, again, I really want to thank you for the opportunity to speak today, and I was really pleased how much I agreed with so many other people who have spoken, but, again, on behalf of our center, I really want to express our support for the FDA and our hope that you will have the resources that you need and that we can help to make that happen.

MR. BARNETT: Thank you, Dr. Zuckerman.

Jeff Bloom?

MR. BLOOM: Thank you.

Just to be clear, I am not testifying on behalf of the Patient and Consumer Coalition today. I am a member of it, but I am here on behalf of Title 2, the T-2 Community AIDS National Network. I am an AIDS advocate and also a person living with AIDS for the last 14 years. So I fully understand the benefits of pharmaceuticals. I wouldn't be here today without them, but I also fully understand the dangers. For people that think that we have to wait to see what is going to happen, for disasters to happen, we are seeing them already now.

Particularly with the AIDS drugs right now, we have a situation where you can take a number, you can pick a number. Some people say 50 percent. Some people say 70 percent. It depends on the clinic you talk to. But it is safe to say that about half the people that currently are in AIDS care are going to see the doctor from the side effects of the medicines that they are taking. These are the medicines that are supposed to be making them well.

No one could have foreseen this at the time of approval because we just don't have that information. It is impossible to extrapolate from 24 weeks of information on 1,000 people what is going to happen when tens of thousands of people take medicines for 5 or 10 or 15 years, and it could very well be a Faustian bargain that we have. I take these medicines. I know what they are doing to my cholesterol. I know what they are doing to my triglycerides. It may very well be giving me heart disease, liver problems, kidney problems in the future. It is a great bargain in the short run, but we really need to find out what is happening in the long run.

There are two things about PDUFA that are

extremely troubling. This should be said over and over again. The person from Scripts had asked the question before about what was the Patient and Consumer Coalition position on PDUFA. I don't believe we have ever opposed PDUFA.

I think what we have said, and what I will reiterate today and I will say as Yogi Berra said deja vu all over again, PDUFA represents fundamentally the Federal Government's failure to fund the FDA adequately to protect the public health and safety of the American public.

We have three pillars of public health in the United States. We have NIH which, to the Government's credit and very much in the correct way, has continued to increase their funding, with the goal of doubling NIH's funding in the next decade, to provide all of this innovate research, to get better medicines, to get better products, to get breakthrough therapies out to people. We have the CDC which gets funded at a tremendous amount of money to do their role, and then we have the FDA. It gets about $24 billion. I am not sure what the CDC number is, but it is up about that.

The FDA's budget is $1.4 billion. That is $1.4 billion to regulate a $270-billion

pharmaceutical industry. One of the problems with PDUFA is it sort of makes the FDA look like it only regulates drugs. That is such a small part of what they do. They have such a broader mandate, and now the focus is it looks like it is a drug approval agency with disregard for the rest of the things, and there has to be greater congressional funding for the FDA.

I do not know if additional user fees are the answer, but these things need to be done. They are not getting done. Even if the post-marketing trials and the confirmatory trials that the companies are doing or agree to do or sometimes do under the current things, the patients are still not getting the information. The third-party payers, the care-takers are not getting the information about how to use these drugs properly with patients, and that is still a problem.

The interesting thing is that the PDUFA has created drugs and gotten them out to the market at a faster rate. There is no question about it, but the question is at what cost, and we are starting to see that cost now.

We don't have a good handle on that cost because we don't have a good adverse event

reporting system. We don't have good post-marketing studies, and we don't have any of these things. It is good to hear the FDA being very candid about these problems, and I appreciate them being very forthcoming about the situation that this has created.

A perfect common-sensical thing here that should be apparent to anyone in this room right now of why having a strict stricture on PDUFA funding only going for drug approvals is the current situation we find ourselves in now. We are at war. We have a bioterrorism problem. The FDA is involved in this situation.

Right now, they can't take any of that money in this emergency situation and take those funds and use it for the public health because it has to be allocated to only drug reviewers. That makes no sense whatsoever.

Something has to be done to give the science back to the scientists. The FDA needs to not be a political institution, but a scientific-based institution, based on science, and let the scientists at the FDA make the decisions, not artificial time deadlines, not artificial performance goals that are not realistic, and,

unfortunately, at the time they were negotiated, did not quite seem to be the way they were. The meetings and time deadlines have turned out to be an extraordinary burden that are not paid for right now, and that is something that needs to be addressed.

One of the interesting things is that the tools for all of this are already there, and I am going to read a small section because I don't think you can divorce the two things. As much as industry would love to have a conversation about PDUFA without talking about FDAMA--they didn't have that problem in '97 when the two were linked together.

I am going to read a section of FDAMA to you. It is just food for thought because this is really what we need. This is a section of FDAMA that talks about the activities that should be done, and this is the conduct of state-of-the-art clinical and laboratory research for the following purposes: (a) to increase the awareness of the new uses of drugs, biological products, and devices; two, ways to improve the effective use of drugs, biological products and devices; and, three, risks of the new use and risks and combinations of drugs

and biological products; (b) to provide objective clinical information to the following individuals and entities -- and this gets to what the Blue Cross person was talking about, which I think is incredibly important -- health care practitioners and other providers of health care goods or services, pharmacy benefit managers, health maintenance organizations or other managed care organizations, health care insurers or governmental agencies, and then consumers, and also to improve the quality of health care while reducing the cost of health care through the appropriate use of drugs, biological products or devices and, two, the prevention of adverse effects of drugs, biological products, and unnecessary hospitalizations, the conduct of research on the comparative effectiveness and safety of drugs, biological products, and devices.

Now, you might think since this is in FDAMA that that would be FDA's mandate, but that is not FDA's. This is the CERTS. This is the Centers for Evaluation and Research in Therapeutics that are supposed to be doing this, but this is what patients need. This is what the third-party payers need. This is what the insurers need. This is the

information that we need that with this faster approval that we need to have this information on the back end, and perhaps the FDA, if we can't convince Congress to fund the FDA more fully to do these things, perhaps they will fund an independent organization like the Centers for Evaluation and Research in Therapeutics, which, thankfully, is in here, but this does give us the tools that we need.

Some people are talking about a disaster waiting to happen, and I want to go back to what Dr. Woodcock said on that one slide, and I think that was a very telling slide. There isn't a disaster waiting to happen. There are disasters happen.

When you look at a slide and you see that there is 50- to 100,000 deaths, some of them obviously from drugs, in hospital, that is not even counting nursing homes. That is disasters already happening, and that number doesn't seem so ominous because it doesn't all happen in one day, but you can guarantee if all 50,000 of those people died in one day, there would be hearings on the hill in half-a-second. 400,000 tires blew up. They had hearings for 3 weeks. 50,000 levers explode. No hearings at all. Part of that is industry probably

needs to take greater responsibility for the safety of their products. I don't know if user fees is the answer. There might be some other roles, such as after a drug is approved that there is a fee attached where there is some post-marketing and safety things that the company has to pay for.

There is no question that the FDA provides the pharmaceutical industry a tremendous opportunity for profit and growth, and they are the last hurdle before they get through this. Yet, they are the least-funded part and the most important part. This has to change.

One of the things that has always disturbed me is that it is really wonderful and I think it is great that the United States is first now in the world in approving all of these things. That also means, though, that there have been thousands and thousands of patients, including myself and many other people probably sitting out here, that have volunteered to participate in clinical trials. We are willing to be guinea pigs. We are willing to take the chance. We are willing to take the risks because we have no choice.

If you have a serious or life-threatening illness, you don't have a choice but to take this

gamble, but it should be an educated gamble.

One of the things that has always been troubling is after you are in this 24 weeks of a trial, that is it. You are gone. You are a piece of data, and you are gone, but nothing is done to track people. There is this valuable database of patients out there that could be tracked more, that could be a subset from the trials, that are followed over a period of time, where we can find out what the events are. There is no possible way of having a crystal ball to see what is going to happen with the drugs 5 years down the road.

No one could have predicted that protease inhibitors, which in 1996 revolutionalized AIDS, now, 5 years down the road, would be causing lipodystrophy, fat redistribution, diabetes, osteoporosis, cholesterol, triglycerides. All of these other side effects were unforeseen at the time, but we don't have good information on it because we don't have a good system, and it has to be funded. Whether it is going to be user fees or congressional appropriations or funding to the Centers for Evaluation and Research in Therapeutics, if it is not done, the only people that are going to lose are the patients, and the

patients are paying the price now and the third-party payers, insurers, and the Government is paying the price.

It is interesting to have these conversations in abstract, and there is no question--I talked to PhRMA last week, and I met with them. I must say, some of their things are very interesting. They would like to have a clean PDUFA. Their position is that if they could have the 1997 PDUFA rolled over, 2002-stamped, passed, they are happy with that. Obviously, they are. They have got the best situation. They have cherry-picked the plum of the thing. They pay for only when a new drug application goes in. They don't pay for any other stuff that the FDA does, for all the pre-meetings, all the consultations, all the up-front meetings that they do, including when they stop developing a drug, wasting millions of dollars, saving the industry potentially millions, if not billions, of investments.

If it cost $802 million to develop a drug, which no one believes that number, but that is the latest number, the FDA, when they help industry in consultation with them prior to filing an NDA to stop going down that path, is saving millions and

millions of dollars. That is never recognized.

CBER and CDER right now review over 5,500 protocols a year for clinical trials. No one is paying for that, and that number is only going to increase. We have more and more foreign clinical trials being done, more and more foreign productions. They don't have inspectors for this.

Out of 30,000 clinical trial sites, they only inspect 1,100 a year. That means at the current rate, it would take 30 years to inspect every clinical trial site. So, yes, there has to be more money.

Whether it is user fees or not, I don't have an answer for that now. I have some qualms about having more industry money in the FDA, but the need to have more information after drugs are approved is vital in order for patients, doctors, third-party payers, and everyone else to know what is going on in their bodies, what is happening to their health, and what are the long-term effects of the consequences of this accelerated approval.

MR. BARNETT: Thank you.

Judy Cahill.

MS. CAHILL: Good morning. Thank you very much for the opportunity to be here. I do

appreciate the agency taking the initiative on this to pull together stakeholders.

I am here as the executive director of the Academy of Managed Care Pharmacy. The academy of a professional society representing the interests of pharmacists who practice using the principles of managed care. They are directly involved with the oversight of building of networks that provide prescription drugs access to over 170 million Americans in the country.

AMCP believes extending the PDUFA user fee program is a necessity. The program has made a significant contribution in securing the financial resources to expedite the Food and Drug Administration's drug and biologics review and approval process.

My comments today will focus on whether PDUFA should also allow the use of user fees for the purpose of monitoring safety after a drug has gone through the approval process.

My observations are drawn from the academy's 4,800 members who have the responsibility of pharmacy benefit management for the American population as a whole.

Those pharmacists are employed by health

plans, pharmacy benefit management companies, integrated health care delivery systems, third-party administrators, and retail pharmacies. Their views are reflective of what the profession of pharmacy encounters in the ambulatory setting.

The fundamental goal of the agency is to promote and protect the public health by determining in a timely manner a drug or biologic safety and effectiveness based on clinical research and taking appropriate action on the marketing of these products. It is that latter charge to the agency that we want to focus on this morning.

The academy believes the objective of FDA's post-market surveillance program must be on the ongoing collection and review of data related to problems associated with a drug's use in order to determine if that drug should continue to be allowed to be marketed to the public under its original approval or whether it should be modified based on experience in the post-market environment. Those might include restrictions on distribution of the drug or it might go to the point of actually withdrawal, which we have heard a lot about this morning.

Consequently, we consider post-market

surveillance to be an essential programmatic function for the agency if it is to fulfill its mission of promoting and protecting the public health.

Pharmacists in the ambulatory setting depend on the FDA to perform its post-market surveillance responsibility for four principal reasons. First of all, the agency is in a unique op to be able to collect that data. Secondly, the expanded experience which we have heard referenced several times this morning that is available in the post-market environment is crucially important for understanding how a drug affects people. Thirdly, what we learn from post-market surveillance data is essential in enhancing patient care. Fourthly, it is also essential in reducing the cost of that care.

Let's take a little closer look at each of those four items. First, the agency's ability to aggregate data, in the inpatient setting, there is the institutional structure that provides a mechanism to collect data on drug use in a systematic way. The highly fragmented nature of health care delivery in this country defies a systematic aggregation of adverse drug events in

the ambulatory setting. Only in the most highly integrated health care organizations are there structures and processes in place to allow reporting, collecting, storing, and analyzing of adverse event data that arise from a single organization's covered population.

Notwithstanding what integrated health care organizations may be able to do, the reality is that most health care organizations look to the FDA to provide vital post-market surveillance data. Even integrated delivery systems must rely on FDA data to validate the observations that arise out of their own patient population.

Second, the data collected after approval is arguably more important than that collected during the drug approval process. The information gained from clinical trials and pre-approval is limited. Studies are conducted in small populations under strictly controlled parameters. It is only when the drug is in the marketplace being used by a sizeable population over a prolonged period of time that the effects, attributes, weaknesses, and problems that are associated with the drug can truly be evaluated.

Third, post-market surveillance data are a

vital source of information that health care professionals use to enhance patient care.

I will turn to the managed care setting for an example of that because there is no more efficient way of approaching total patient care than in the integrated health care delivery system.

Integrated delivery systems share post-market surveillance with the prescribers who are under contract with them. They are able to reinforce what the FDA has issued in its Dear Doctor letters, and they are also able to take that information and to adapt to their practice protocols that are used by their providers to enhance patient care.

Additionally, pharmacy and therapeutics committees employ post-market surveillance data as one factor in determining whether a drug should be recommended for use by its patient population. FDA reports allow the committees to validate patient reaction within their own populations, weigh the potential harm of a drug, for instance, its potential benefit, make informed decisions about inclusion on the formulary, and identify high-risk patients who need to be targeted for specific case management review because of what has been learned

about a drug's reaction.

Fourth, problems associated with a drug's use directly impact the overall cost of care in this country. Numerous studies in recent years have demonstrated that many physician visits, hospital admissions, emergency room visits, laboratory tests, expenses across the spectrum of health care expenditures in this country result from improper use of drugs or inappropriate reaction to the use of those products. Clearly, a post-market surveillance program helps avoid adverse drug events and can, thus, save our health care system significant dollars.

But where does that responsibility lie for post-marketing surveillance? I would submit to you that the Federal Government, drug manufacturers, and prescribers all have responsibility and obligations regarding post-market surveillance.

Until relatively recently, the programs of the FDA were almost entirely focused on the drug approval process, and from what we have been hearing this morning, that still is certainly the primary emphasis. To some extent, that has changed, and we greatly support the move to greater and more comprehensive post-market surveillance.

Legitimate questions can be raised as to whether the agency has been able to implement effective post-market surveillance.

I was quite taken aback to find out that the MedWatch program is staffed by three people. Something needs to be done, definitely.

Similarly, drug manufacturers must recognize their obligations to assure throughout the life cycle of their products the safety of all of their products and that they must be accountable to both the public and to the regulators in providing those assurances.

Prescribers. Prescribers are in the most critical position for assessing the problems associated with drug use because of their direct interaction with patients and because of their overall responsibility for monitoring and directing patient care, the need to better understand their responsibility for reporting drug safety problems. Unless the prescriber becomes far more engaged in the post-market surveillance process, its potential for success will be limited.

The FDA must use its resources to encourage far greater reporting by the prescriber. FDA, manufacturers, and prescribers must be far

more proactive in the gathering, evaluating, and disseminating of information about drug safety after market approval of a product.

I would like to conclude by issuing four recommendations from the Academy of Managed Care Pharmacy. First, FDA's current post-market surveillance system for identifying previously unknown adverse effects of drugs suffers from a lack of resources. A new user fee imposed on manufacturers should be added under PDUFA and should be designated for an approved and coordinated post-market surveillance program. Such an earmarked fee is appropriate, given the manufacturer's responsibility to provide a drug that is both safe and effective throughout its entire life cycle. The funds collected from user fees should be of an amount sufficient to recognize that post-market surveillance is as important as the drug approval process is.

Secondly, prescribers, pharmacists, manufacturers, and health plans are remiss in reporting adverse drug events and other problems associated with a drug's use. The FDA should initiate an aggressive educational campaign targeted at patients and health professionals,

stressing the importance of and encouraging the reporting of adverse drug events and related problems to the agency.

Thirdly, the FDA should undertake an audit of the notification mechanisms it uses to ascertain if all parties with a need to know are being informed; that this is happening on a timely basis and with sufficient and detailed information and appropriate opportunity for feedback and input.

We do hear from the members of the Academy of Managed Care Pharmacy that frequently pharmacy directors and health plans do not receive from the agency notification about what has been discovered in the post-market surveillance. They generally hear it from one of the doctors who has received the Dear Doctor letter, and this overlooks an opportunity to get out to a vast network of health care professionals.

Fourthly, we suggest policy-makers consider the alternative of creating an independent organization responsible for post-market surveillance, separate from the FDA. The public agency would collect, analyze, and disseminate information about the safety and efficacy of drugs in use in the marketplace. The arrangement would

be similar to the one that exists between the Federal Aviation Administration and the National Transportation Safety Board. Both the FDA and the post-market surveillance agency would serve the public in assuring that safe and effective drugs were available. A separate agency would provide significantly higher visibility to post-market safety issues and be independent of the decision-making process that originally approved the drug for marketing to the public.

The separation of pre- and post-approval functions would enable distinct, independent assessment of the critical issue of product safety.

The Academy of Managed Care Pharmacy supports changes that would result in a significantly improved and comprehensive program for identifying problems associated with the use of drugs by patients.

We look forward to working with the agency and any other public authority in achieving that end. Thank you very much.

MR. BARNETT: Thank you.

It is time now to once again open the floor for comments, and if you have any, come on up to the microphone. Remember, these are comments on

the post-market aspects of PDUFA.

Just identify yourself.

FLOOR QUESTION: I am Susan Cohen, and I am a consumer member of an advisory panel. So I bring my dimension to this. I usually have a loud voice.

I have two concerns about the approval process. One is I am concerned about the conflict of interest when a researcher receives money from a pharmaceutical companies and then speaks on behalf of the product, and I am also concerned that the medical officers get all the respect they possibly can because they provide us a lot of information.

I also feel very strongly that any insert that you get with medication or from the pharmacy, that they give you a number to call if you have an adverse effect, and it should include some questions so people have some parameters in which to do that.

I think that there should be a separation out of drugs that are already on the market, and this is just one more drug that does the same thing. First, it is something that is entirely new and very special. I think there should be a separation out of that.

I am also concerned that in the process there is not enough testing of children because so much of these drugs go on to children, however it is done. I think we need more of that.

I also am concerned that the consumer really understands what the advertising means. That is why I want to see on a bottle a label that gives them the phone number to call and really points out the specifics because the end product of this from my point of view is not money. It is about the consumer and how they can be protected.

I know we have talked about recalls. Do we know how many recalls there were under PDUFA, the process of PDUFA, how many?

Dr. Woodcock, do we know?

DR. WOODCOCK: Well, we know the rate. The exact number changes over time, but the rate of recalls before PDUFA of new molecular entities, new products introduced into the United States is 2.7 percent of all products introduced were recalled.

Under the user fee program, it is 2.8 percent of products that have been approved under the user fee program have been withdrawn..

FLOOR QUESTION: I am just curious since the PDUFA process is different than the other

process I have seen. Are the questions unique to the process of doing PDUFA that you wouldn't normally ask on the usual process?

Well, I think that is something that should be considered. Thank you.

MR. BARNETT: Thank you.

MR. BLOOM: Could I make a comment about what she has just said?

MR. BARNETT: Yes.

MR. BLOOM: Excuse me, ma'am. Ms. Cohen, just to reemphasize something that you brought up, which I think is an excellent point, about a number on the bottle in terms of adverse events, one of the things that we have talked about at the Patient and Consumer Coalition meetings--and it is not a formal position that we have yet, but I think that your point is excellent.

One of the things, we are stuck with this world of DTC advertising and television advertising and this plethora of marketing now. Your point is extraordinarily well made in that how can we use this DTC advertising for the betterment of patients as well. One of the things that we think that would be very useful is to do exactly what you are recommending. It is to have a number on there, to

have an information thing to say if you have a serious adverse event or if you have any questions or problems with this medication, call this number, report what happened, so that there is more information coming in and more reports because we do capture such a small thing. So it is an excellent, excellent recommendation.

FLOOR QUESTION: And the print should be larger.

MR. BLOOM: Absolutely.

FLOOR QUESTION: For people who are older--and I am an old lady, I can tell you--on the television there is something that flicks by your eye. You don't know what it is, and also in the print in the paper, since you got me going.

MR. BLOOM: It should be in everything. I agree with you. That is a great idea.

MR. BARNETT: Yes, sir.

FLOOR QUESTION: Hi. Ben Peck with Public Citizen.

One of the comments that Diana Zuckerman made about how the adverse reactions as a result of Fen-phen were discovered prompted me to think about a recommendation that is referred to in a GAO testimony about the creation of sentinel sites

where drugs would be released to specified sentinel sites where their adverse reactions could be monitored more carefully.

I was wondering if I could get reactions from Dr. Woodcock or others on the FDA panel about their views on that sort of process being created.

Then, also, I would love to hear reaction to the idea of an NTSB-like setup for the post-marketing surveillance process that the last person on the panel talked about.

Thank you.

DR. WOODCOCK: With regard to the issue of sentinel sites, that whole idea is part of a broader issue of should we have some active surveillance, which is something we don't have. We have to all be aware of that. We do not have active surveillance of adverse drug reactions in the United States, and we have passive surveillance. We hope somebody will send a report in, and if they do, we will find it.

It works pretty well for the extremely rare, startling, unexpected adverse events, and we do find those pretty quickly, but as was point out, there is a whole range of adverse events that occur and we also don't know the rate. That is the

biggest problem with passive reporting. We just know that a few occurred. We don't know how many actually occurred, and we don't know how many people were taking the drug, and at risk. So we don't have that rate information or comparative information. Well, it is bad for this drug, but if you read about it in the paper, you start reporting. But what about all the other drugs? Are they worse, actually? We just don't know about it?

So we have looked at this, and, actually, in the recent appropriation, there is some money for the device center. We thought we should start there, as it is the greatest need, and they have already had some pilots of something called MedSun. That would be hospital-based, but it would be promoting a more active surveillance through education of the clinicians there and giving them a computer system to report through and so forth.

We would hope that we could more generalize that effect if that pilot would be successful and add drugs in biologics, and, of course, for those we would have to add other settings because, although the reports are from hospitals because they are all collected together,

we think most of the action is out in the outpatient world.

MR. BARNETT: Okay.

FLOOR QUESTION: Hi. Jay Lee from the National Center for Policy Research for Women and Families.

Like Dr. Griffin, I was very pleased to see that the President recently signed a measure increasing the budget for monitoring patient safety and adverse event reports from 48- to $58 million, but I was also dismayed to see that the estimated revenue from PDUFA in this coming fiscal year was reduced from $162 million to $135 million. So funding from PDUFA may be less reliable than from congressional appropriations. Also, others have noted that PDUFA funding may raise more concerns about conflicts of interest.

My question to both the FDA panel as well as to the panel of guest speakers is: Should certain elements of post-market surveillance in PDUFA III, assuming that PDUFA III does fund such things, be funded exclusively or primarily by congressional appropriations while other functions are funded primarily or exclusively by PDUFA III?

DR. SUYDAM: I think that is the critical

question we are here to discover your and other points of view on. I think it clearly is an issue for us.

The reason the PDUFA number went down was because of the formula that is used to determine how the funds are allocated, and the fewer number of applications we have coming in means that we have fewer dollars coming in. The rate of applications coming in from the pharmaceutical and biologics industry has been going down over the last couple of years, and as a result, there is less money to support the program.

I think it is clear that we need to have a more active post-market surveillance program. It is something that we have put in our budget, proposed in our budget for the last 4 years, and, hopefully, this year was the first year that we really had a breakthrough that we got $10 million for it and we hope that will continue.

FLOOR QUESTION: Great. If I may ask one follow-up question quickly. I know money is fungible, but are there currently programs that are funded by PDUFA where certain elements are specifically funded by congressional appropriations and others in that same program funded by PDUFA?

DR. SUYDAM: No.

FLOOR QUESTION: So there is no separate issue at this time.

DR. SUYDAM: The way the program was set up, we--am I right on this?

DR. WOODCOCK: Yes.

DR. SUYDAM: I am. The way the program is set up is that there would be no specific program that would be PDUFA only. So you have the flow of money comes into the drug center, and you have it paying for a percentage, for example, of the library services or a percentage of the IT activities, but you can't tell which percentage or what activities. It is not specifically designated for that.

FLOOR QUESTION: In PDUFA III, I would suggest that there be more careful accounting of that.

Thank you very much.

MR. BARNETT: Thank you.

FLOOR QUESTION: My name is Niki Colton [ph], a health care attorney in the area.

My question is with all of these suggestions, we are looking at a go-forward issue, and if we are depending on PDUFA, it would be

prospective for new drugs, new applications, and the revenue of that is uncertain.

What is the suggested strategy for the drugs that are currently on the market, protease inhibitors, for example, as to how do we catch up?

MR. BLOOM: I will take it. How will we catch up? How we will catch up is Congress and the Federal Government has to live up to their responsibility to fund the FDA properly, and if they inadequately fund it--I am floored. I would like to see a show of hands, just out of curiosity. Let me take a little random survey here.

MR. BARNETT: Hey, who is the moderator?

[Laughter.]

MR. BLOOM: I am now.

MR. BARNETT: Go ahead.

MR. BLOOM: In this room, how many people here--raise your hand if you think that three people in the MedWatch program are an appropriate number of people to have to be overseeing adverse event reporting for the FDA?

DR. WOODCOCK: Well, Jeff, let me clarify what the three people do. They take the direct reports.

MR. BLOOM: Right.

DR. WOODCOCK: We have a group of people, and then those are put in the database by our contractors. Then our safety evaluator looks at them, but my point is to have a robust program to teach clinicians, pharmacists, everyone, the importance of reporting, to run that outreach, to make it easy.

We had some Members of Congress who tried to file reports on our computer screens a while ago, and they weren't able to do it because it isn't that modern. That is the kind of thing I am talking about. We need an outreach program. We know.

We ran one about a decade ago in Rhode Island, and we increased the volume of reports, I think, 17 times. We got 17 times more reports by publicity, teaching, training people to report. Now, I don't know what we'd do with 17 times more reports. We are swamped now, but the point is in that outreach and handling the direct reports program, there are three people.

MR. BLOOM: Right. That same situation happens at the FDA with DDMAC, the division that oversees all of the advertising. They are incredibly inadequately staffed in relation to the

volumes of new DTC, television, print, media. There are 70,000 drug detailers that visit doctors' offices. Thanks to PDUFA, there are 1,000 less non-PDUFA employees at the FDA, down to 7,000 people that work on other things. The disproportionality of this is staggering when people think about it.

So the bottom line is that it is very good that we are having this meeting here today, and it is a good discussion to have, but this is the message that has to be carried to Capitol Hill, to Congress, and the administration that they absolutely, positively must start funding the FDA or the CERTS or some other function, like an NTSB thing.

We are not opposed to the independent safety board. We think it is a good idea in some ways. To have this happen--because we are losing this information. We are getting further and further behind every day, and we are putting more and more new drugs on the market without the systems in place to still get the information, and that is the real issue here. People are putting these things in their bodies every single day, and we really need to know what happens, not just this

year or next year, but 5 years and 10 years and 15 years, and we don't have that information in a good way now. It is a matter of appropriations, and the dollars have to be put up for it.

MR. BARNETT: Thank you.

Yes.

DR. ZUCKERMAN: I just wanted to add to that. We are in the ironic situation of having a Vice President whose life depends on an implanted device that may or may not be having any kind of rigorous post-market surveillance, but, also, of course, I would assume a lot of Members of Congress now taking cholesterol-lowering drugs and other drugs for chronic health conditions. One of the things that would be helpful would be to have the information available for those of us who--of course, we do not lobby, but educate Congress to let them know that the drugs that they themselves are taking, to let them know what the resources are currently available to check on the long-term safety of those drugs once they have been approved. I think that would be a very valuable lesson that would hit close to home.

MR. BARNETT: Anyone else? Yes.

FLOOR QUESTION: I am Ann Rose. I am

president of a company that specializes in helping the biotech industry and small pharmaceuticals who are mainly research-based, help them in their development so they have credible proof of concept, Phase I trials, so that, as Jeff said, we don't have more patients exposed to potential harmful devices or drugs.

But I am not here on that behalf today. I am very much interested in the discussion that went on, and Judy made a comment that I think elicited in my mind the following, and that is that responsibility can be shared across all fractions. Whereas, FDA needs more assistance, and I had been in the Department in prior years for a good number of years, understand the FDA issues, I think, at least to an informed consumer point of view.

There is responsibility for all the organizations, managed health care, insurers, et cetera, who have direct contact with their members to inform them to report the adverse experiences they are seeing.

I was appalled when Janet put up the small number that comes from this type of reporting, and there is a responsibility for each of us in our roles and those particularly in the organizations

that are dealing with that to spend a concerted educational effort at doing just that.

Secondly, I think Jeff hit on a point that is also close to my heart, and change comes from advocacy groups. I happen to have been in the administration when AIDS hit the public health. A large measure of why there is change and why there was change in the FDA and in Congress had to do with the vocalization. So it is not, in my mind, good enough for us to sit here and bitch and complaint about Congress not going it. We have a personal responsibility to make that cause known, and I think the AIDS issue, as Jeff knows, did miraculously different things in the entire approval process.

MR. BARNETT: Thank you.

MR. BLOOM: I thank you for that comment, and I want to support what you said. I think you are right. Everyone does have a responsibility, and patients even have a responsibility.

I can give you a very small example that sort of gives you a broader perspective of this, and this is a very small example, but it shows you exactly, to highlight her point.

I went to the doctor about 2 years ago and

I had ingrown toenails. It was sort of a strange thing to sort of suddenly have. I was sitting there with the doctor, and they asked me if I was on a particular medication. I will leave the name of the protease inhibitor unstated for the purposes of this meeting, but suffice it to say, he said, "Oh, you are the fiftieth person that has come in with ingrown toenails that has been on this medication." I said, "Well, have you turned in any of these reports to the FDA?" He said, "No. I didn't think about that."

There may not be a cause-and-effect there that there is 60 patients at one podiatrist office that all have ingrown toenails that are on the same drug, but there is a good bet that there is some relationship there, and he turned in those reports.

But you are right, it is everyone's responsibility, and it is everyone's responsibility because you do have to press your doctors to turn in the reports, but, also, I think Janet can tell you that is another thing about getting MedWatch and all of these things put up more is patients can report these adverse events themselves, friends of patients, their family members. So the ability is there. The effort has to be made. The public

effort has to be made to broaden it and to make it more important, and perhaps the FDA is not the best place to do this. The CERTS might be. The CERTS are going a fairly good job of this right now. Maybe Congress will be more willing to fund them. There is some reluctance, obviously, on Congress' part to feel that the FDA should be funded. They don't like regulatory agencies. Unfortunately, regulatory agencies exist for a reason.

We have them because they are regulators. They are here for a purpose. They are here to make sure that drugs are safe and effective and do what they are supposed to do, and Congress tends not to like regulators until things go wrong and then they come up and say, "All these tires blew up." Well, you didn't give any money to the NTSB to do anything about this.

So we would like to try to prevent the disasters, but you are right, it is everybody's responsibility, and I totally agree with that.

MS. CAHILL: I would just like to underscore the point that the questioner raised and that Jeff underscored and, Janet, that your figures speak to direct reports. I identify what I hear from a number of my members who are pharmacy

directors in large health care networks that have thousands of physicians under contract, and when they go out and have face-to-face meetings with their physicians about what they have experienced with given drug products, by and large, they hear what Jeff heard from his podiatrist, "Oh, no, I just never even thought about reporting that. Oh, yeah, I see that all the time." And it is that type of lack of consciousness that I think would underscore the need for an educational campaign.

I was impressed by what you had to say, Janet, about what happened in the Rhode Island pilot experience. When you start talking to people about these things, all of a sudden, it begins to interrupt the cycle of normal operations, if you will, and people start attaching the importance to it that needs to be.

MR. BARNETT: Please go ahead.

DR. GRIFFIN: The only other comment I was going to make to follow on, a lot of it goes back to the money train, and it goes back to active versus passive surveillance. Passive surveillance is obviously a lot less expensive. You sit and you receive whatever reports you can get. Given past levels of funding, passive surveillance is

essentially what can be done.

Moving to active surveillance, where you go and you look for certain things, if someone is placed on a drug that you would expect to be a permanent medication and they don't renew it after 90 days, there is a hint in there that, well, either they didn't like it, they had an adverse reaction, or they were changed to something else, but then the question becomes why. To be able to go after that, though, takes funding, and the funding needs to be stable funding, not tied to the portico winds that happen to blow from year to year in the way our budgetary process sometimes works.

MR. BARNETT: Thank you.

FLOOR QUESTION: I am Jill Waxler. I am the Washington editor of Pharmaceutical Executive magazine and some other magazines in this industry.

Just to clarify, everyone agrees that FDA should have more reliable funding to do a lot of post-market surveillance and other safety-related issues, and there have been various proposals. One can assume that Congress would probably never supply all the funding for all the various proposals that everyone has.

Does this panel and other people who have

talked see that the preferable option is for the manufacturers to pay more user fees for FDA to have more flexibility and control over how they use a specific finite amount of user fees or for some of these activities to be handled by a totally separate agency as some people have referred to?

MR. BARNETT: Before anyone answers, let me just remind you that we have about 5 more minutes before lunch.

Do we have a response to this?

DR. GRIFFIN: The first one is, obviously, we get to certain places by drifting different lines, but we have to acknowledge where we are. To create a new agency or a new safety board or other things would add even more to the cost, and I think it is a little purgative to the Food and Drug Administration which I think has done a very good and a very impartial form of dealing with the resources that they already have allocated.

The funding goes back to where is the money going to come from and how do we make sure that it is a stable source. User fees might not have been my initial choice when building it, but certainly going forward, we look at where we are and I think it is the best vehicle to tie future

funding to.

MS. CAHILL: I think that there ought to be serious consideration of an independent safety board, and that is not to cast any aspersions on the job of pre-approval that the agency is doing.

I, for one, as I look at the track record that the agency has, am very impressed by the independence from the manufacturers that the agency maintains. The suggestion for an independent safety board is rooted really in the observation that medicine is not a science, it is art to a large extent. So, if you do have two parallel bodies that are looking at drug products, you are probably better assured of getting a reasonable assessment of the safety of a given product. I think that that underscores some careful looking at whether or not there should be an independent safety board set up.

DR. ZUCKERMAN: I just wanted to add something. I just think the whole issue of conflicts of interest is a very complicated issue. We can say that ad nauseam, I suppose.

In the ideal world, certainly, I think user fees raise an appearance of conflict of interest and perhaps a sense that companies are

paying for approval as opposed to paying for review, and I think that is an appearance problem. Of course, it is also true that medical devices are not paid for by user fees, and I don't think anybody would say that that seems to be a system that is working better or has fewer conflicts.

I think there are a lot of conflicts of interest in medicine and in regulatory review. We all know that people work at the FDA and then go to work for the companies that they previously reviewed. So this is a big issue, and I think that user fees are just a small part of a much bigger issue. So, before we solve the problem by getting rid of user fees, I think we probably need to look at more direct conflicts of interest of individuals who do reviews or participate in reviews and the whole advisory committee process that includes people who have potential of financial links to the products and so on.

I also just want to say that having worked in Congress for a dozen years or so, I think that Congress could be persuaded to be much more generous and appropriate in their funding of the FDA. I think it will take work to make that happen, but I absolutely believe it is possible,

and I also know that Members of Congress and their staff don't understand the FDA. They don't understand what you do. They don't understand why you are important, and that is a job that you all have to do better and we all have to do better, too.

Thank you.

MR. BARNETT: On that hopeful note, yes, another one.

DR. WOODCOCK: Sorry. I just had two comments I wanted to make, but I forgot one of them.

Oh, yes, I do remember. First of all, the Center for Drugs has established a separate office of drug safety that recently happened that is independent. It has an independent reporting chain very high up in the organization, independent from the pre-market side.

Second, I would just like to say vis-a-vis all this, the panel really struck at a number of issues. I think the source of the greatest professional frustration I have had in working at the Center for Drugs for the last seven years is our inability to get this information that is needed in the hands of the people who need it in a

way that is timely and that is useful and is preventive of problems happening. We need to work everywhere. Managed care, managed care pharmacy, the patients and the consumers, and the physicians need this information in a way they can use, and it is very complex why you don't have that information. It is a very complex series, but we are working on it.

I don't think it is lack of will. It is just our lack of ability to mobilize the resources to get that information, but that is definitely one of our goals.

MR. BLOOM: Getting back to your question, ideally Congress should be the source of the funding, but if they can't be the source of the funding, you will have to find another source of funding.

Perhaps what we should be calling it instead of Prescription Drug User Fee Act for approval is after a drug is approved, perhaps we should have the Prescription Drug Approval Act, that after the drug is approved that they pay fees for post-marketing and safety because they are certainly making the profits after the drug is approved, and that is a source of funding.

The question is do they have a responsibility once the drug is out on the market for the safety of their product, and I think most people would argue, yes, they do, except for the companies because they seem to think they don't.

MR. BARNETT: Okay. Thank you very much.

We are going to go to lunch now. I have 12:10. There is a restaurant here. Let's make it one hour. Let's make it 1:10 back here.

[Whereupon, at 12:12 p.m., a luncheon recess was taken, to reconvene at 1:19 p.m., this same day, Friday, December 7, 2001.]

A F T E R N O O N S E S S I O N

[1:19 p.m.]

Panel III - Finance

MR. BARNETT: We are ready now for our third and final panel PDUFA, this one having to do with the financial aspects of program.

Our FDA representative this time is Theresa Mullin who is associate commissioner of the Office of Planning in FDA, and our non-FDA panelists--and, again, I am going to go in the order that they are on the agenda. Just raise your hand when I call your name. Mary Rouleau, deputy legislative director at the United Auto Workers; Sharon Levin, associate medical director for the Permanente Medical Group, Diane Dorman, senior director of public policy with the National Organization for Rare Disorders, and Mike Warner, vice president for Bioethics at the Biotechnology Industry Organization, or BIO.

We will start out with Theresa.

MS. MULLIN: Good afternoon. My name is Theresa Mullin, as Mark said. I am the associate commissioner for Planning at the Food and Drug Administration, and this third panel is going to focus on questions of funding versus performance

for FDA's human drug activities and what we might call the fundamentals, which we have been talking about I think throughout the day, of PDUFA.

Based on our experience with PDUFA I and II, we know that these fundamentals need to be in alignment for the program to work as intended. In PDUFA II, FDA has learned that there can be a fair amount of uncertainty on the funding side of the equation, and we need to find a way to balance that against the predictability that stakeholders want from FDA in meeting previously set performance goals.

Although we have, by and large, delivered on the promises for those performance goals, we think that we are now seeing some side effects of the uncertainty on the resource side, and going forward, we would like to find ways to ensure more stability and/or flexibility on both sides of these fundamentals to keep them in balance.

Before the enactment of the Prescription Drug User Fee Act in 1992, we had a backlog of new drug applications, and timely review was a problem. PDUFA added resources to supplement. The fees supplemented FDA's appropriation for the human drug review process, and in exchange for the funding for

user fees, FDA agreed to meet specific performance goals that would help expedite the review of the new drug applications. The extra money made it possible to hire review staff and have the information systems to be able to do that.

Under PDUFA I, 1992 to 1997, that exchange worked pretty well. The applications with fee revenues came in, and we were able to hire the staff to meet those deadlines. The time for approval got shorter. Patients got access earlier, and it basically worked.

Under PDUFA II, 1998 to the current day, things have not gone as expected, and the balance between the revenues and FDA's performance obligations, which we had in PDUFA I, had changed unexpectedly in PDUFA II.

This graphic, I think, illustrates pretty well why that is. The user fee revenues are all driven by essentially the volume of fee-paying applications, and as you can see, the first 5 years of the program, to the left of that vertical line, there was a pretty consistent upward trajectory in the number of applications paying fees, but subsequent to that, on the right of that line, PDUFA II, we have had a lot of volatility and a

downward trend in those numbers.

In PDUFA I, we anticipated--and we in the industry, biologics and pharmaceutical industry, the reps we discussed this with and others involved in the process looking at the PDUFA I experience assumed that there would be a continuing increase in the amount of fee revenues ample to fund any increase in performance obligations, and FDA agreed to an expansion of those performance goals in PDUFA II based on those assumptions, but I should say the match hasn't really happened.

What we did see was an increase in the overall work, though, that now was obligated under PDUFA. The top row of these graphics, this is a snapshot of the workload for PDUFA, and then the upper left graph shows the fee-paying application workload. As you can see, that has gone down a bit in recent years. The others have steadily increased across the top, and the four on the bottom of this slide show additional things that FDA agreed to meet in goal deadline from 1998 onward.

These are graphics for meetings with companies to get feedback and guidance through the development of the product, FDA's evaluation of

special protocol questions submitted by companies, responding to clinical holds, and dispute resolutions. We think these are all really valuable activities. We think that these activities have helped to make development more efficient, have helped to reduce clinical development time, and is in the spirit of what PDUFA is supposed to be doing and FDA's public health mission. They do help get drugs, safe and effective drugs, to patients more quickly, but they also do involve a lot of additional work.

The agency has been trying to meet the workload involved here by out-spending, in fact, current collections. If you think about how the fee-paying applications are going down and the effort involved is going up, this graphic is showing what is going on there.

The green bars here are what is being spent, and the beige bars are what is being collected. In 1998, as you see, the collections exceeded what we spent, and in a few other years, we have a little bit of that, fee carryovers that we were able to use in subsequent years to help make the difference up between current collections and what we needed to cover the program costs.

In fiscal year 2001, the difference between what we needed to cover and what we had available from current collections was $22 million, and in fiscal year 2002, based on the formula for fee collections, we think that we are going to exhaust the carryovers because we know that our spending is likely to exceed what we will be able to collect.

That is a particularly bad situation to be in, looking ahead to the sunsetting of the program, because we won't have any money to help keep it going beyond the date when the program ends in September.

Some people have asked us why don't you just make up for the shortfall in fee collections by using appropriations, and this, I think, just illustrates the problem with that and I think it also speaks to the earlier discussion about the relationship between PDUFA and the appropriations and the dynamic there.

The sort of pale purple color along the bottom shows the history of spending on human drug review from appropriations. The dark purple area is the appropriations spent on other activities outside of that human drug review, and this is data

just for the Center for Drug Evaluation and Research.

So all the blue is appropriations, and you can see there is a steady, but modest, increase in the amount of appropriations that has been spent on the process of human drug review. The amount of fees has gone up much more and remains additive, but it is really the amount of appropriations in total that have gone down. That is why it is difficult to take any more from appropriations and put it towards the human drug review process. There are many other critical activities that we need to cover.

FDA's financial goal for PDUFA III would be to get things back in balance. We think that there are probably many alternative ways to bring the agency's performance obligations in better alignment with the available resources, and we would like to hear your views on that and what you think should be considered.

The other thing I might point out on that last slide, those last years were the years of peace and prosperity budgets for us. So we don't know how it is going to be in a period of war and deficits.

So here are three questions that we have framed to hear from you and to hear from our panel. How can FDA ensure that PDUFA goals are met if there continues to be a funding shortfall? If the funding shortfall persists, should FDA, in order to best protect public health, set review priorities, and if so, how? Should there be flexibility in setting user fees to cover the increased cost of the program?

Thank you.

MR. BARNETT: Thank you.

Let's go to our panelists again in the order that they are on the agenda. So, Mary Rouleau, you are first.

MS. ROULEAU: Thank you. Thanks for giving us the opportunity to speak here today, and I also would like to thank you all for keeping the meeting on time. You run a very good meeting here. I like meetings that are run on time. It is very helpful for people who have got tough schedules. So thank you for that.

You got my comments in your packet. I am not going to read all of them because a lot of them have been covered.

I want to point out a few things up front,

and that is that the UAW is a member of both the Patient and Consumer Coalition and RxHealthValue.

I spoke at the September 16th meeting you all had on PDUFA. We were at that point emphasizing some drug safety issues that we were concerned about.

Along with other members of the Patient and Consumer Coalition--and you are hearing from most of us today--we have identified many concerns we have about the user fee system, and I have laid them out there.

I want to reiterate a point that my colleague, Jeff Bloom, made this morning, and I couldn't agree more, which is this is a really interesting and good exercise, but this is the kind of exercise that we really need to have in front of Congress for two reasons. Congress is the appropriators, number one, and, number two, they are going to rewrite or write PDUFA III. They are going to write the terms and conditions for the use of user fees and any other funding schemes they throw in.

So, while I thank you for this meeting and this is important, it is incumbent on us in the audience to understand. The real audience, I

believe, for this meeting is the Congress.

I want to also point out that for the last couple of years, the UAW has joined with other patient and consumer coalitions on lobbying the Congress on the appropriations issue. WE have asked for more money for the FDA, especially for post-market surveillance, protection of human subjects in clinical trials, product and facility inspections, and DTC, and also for fair cost-of-living increases for your very important employees. So we are trying to put our money where our mouth is, so to speak, not that we have been all that successful, but we hope others will join us.

Of course, we are happy to see that the 2002 budget does include an increase, but it is not enough.

Theresa, you just said the goal might be to get things kind of back in balance, and that is important. Yes, we agree with that, but the reality is, folks, we have a problem right now, and we are looking forward and we are designing PDUFA III or lobbying for appropriations. We need to factor in a couple of things that have been mentioned this morning, which is that we expect a

big increase in the number of drugs in the pipeline. So the workload we have now, I believe, is only going to get that much bigger at the FDA.

The second thing is these drugs are being disseminated to the public faster and faster. We are getting older, and we are taking drugs for more things. So this is not arithmetic, if you will. We are looking at a different type of formula here. So it is absolutely incumbent that we understand that as we move forward and design a system that will probably take us at least 5 years out, maybe more.

I need to say as a matter of public policy where the UAW is on this, as a matter of public policy. We think all funding should come to the appropriations process, and that we should get adequate revenues for appropriations through a progressive tax system. So I don't want us to be locked into the idea that we have no choices here but a user fee system.

There are some political ramifications and realities, and we will play to that, the UAW will, but the reality is we could get enough general revenues for the agency and for other important health and safety needs if we had the political

will.

Part of it is, yes, there is a revenue problem and it is going to get worse for a combination of reasons, which I could rant and rave about for hours, but I won't.

One important thing is that there is this Tax Code out there that has a lot of loopholes and deductions, and we have to ask whether people who are benefitting from our system are really paying their fair share. I have said that, so I will move on.

Obviously, if the user fee system is to continue--and let's say it is a 99.999-percent chance that it will--we believe there must be a wholesale revamping of this system.

We would suggest one thing to consider, and I say consider because no one has all the answers right now, but we need to have the dialogue that teases the right answer out. It might be utility model approach.

Now, in the world of public utilities in many States, what they do is they assess the public utilities based on their relative size. The money goes into a pool, and that funds the activities of the public service commissions, but the point here

is that the utilities don't get to blind-item and parcel-out where the money goes. That discretion is left up to a public service commission. We think this is important. We want the FDA to have the sole discretion about how to use this money and where because, if they are not going to do their job, we will be up there lobbying them and lobbying Congress. We have faith in the integrity of that process.

There should not be, for example, some kind of trigger formula like exists currently that requires the FDA to make artificial decisions about spending, merely so it can get its hands on the user fees.

Maybe, perhaps, if the FDA does not receive a budget increase, then the PDUFA drug approval goal should decline accordingly.

Maybe, perhaps, fees should be imposed from the time that the FDA activities with drug companies begin.

So we are calling for a reevaluation of the user fee system. We also believe that the performance goals must be renegotiated with all concerned stakeholders. That means patient and consumer groups should be at the table when we are

designing these performance goals.

I have listed some things that you have already heard--I am not going to repeat them--what should be considered as a part of a redesign of the performance goals, but I will add that I very much agree with my colleague, Amy, from the National Women's Health Network who said maybe it is time to consider performance goals on the public safety aspects, also.

So, in principle, we are opposed to the further expansion of user fees, in principle. However, if this is our fate--and I am betting it probably is--we want to make sure that these fees are used for safety initiatives, subject to the sole discretion of the FDA, without the requirement of collaboration or consultation with the industry or with others.

At the meeting last September, representatives from PhRMA, BIO, and the American Medical Association mentioned the need for adequate FDA funding. Great. We want to work with them on that. This is part of our job. Those of us who are passionate, either for or against user fees, we have another responsibility, and that is to lobby Congress on the appropriations.

One thing that maybe we could discuss in the question-and-answer part, I have come to the conclusion that a big part of the problem--and I don't know the historical reason, and maybe you guys can explain it to us, but the FDA funding, it seems to me, should be in HHS, and that being in the Agricultural Committee is a big problem because you run into staffers over there who have no idea what you are talking about. Let's face it. The farm team in Congress is very strong, and there is good reason for that, but I just think the FDA appropriation does not get proper attention, and I think part of the problem is where the appropriation is housed. Maybe there is a good reason for that, and you can tell me why I am wrong.

Let's go to the questions because I think at this point in the say, these questions are largely rhetorical. How does the FDA ensure that PDUFA goals are met if there is a funding shortfall? Well, it doesn't. You can't.

The FDA has already said that it expects the performance goals to slip because of a resource problem. That is a problem, but, also, and further, it is totally unacceptable--totally

unacceptable that safety issues suffer because of resource constraints.

If the funding shortfall persists, should the FDA set review priorities, this question is purely rhetorical. Of course, it should. It should be looking at the drugs that are for serious and life-threatening conditions or rare disease and for which there is no reasonable substitute. That should get the first priority here.

Lifestyle drugs, "me,too" drugs in our view of the world, UAW, we see the low priority, or should. Should there be flexibility? Of course. If there is going to be a user fee program, it shouldn't be tied to appropriations triggers. Fees should kick in earlier. Protocol for fee-waiving might need to be reviewed to make sure that it is not too generous, and maybe we should look for some new sources, like some of the money that comes from the pediatric exclusivity provision. We know that drug companies are doing quite well in that regard.

Some of the fast-track issues, which you all have publicly said, have drained some of your resources. We should look for additional sources of revenue from the companies.

Thank you.

MR. BARNETT: Our next speaker, again, in the order on the agenda, is Sharon Levine.

MS. LEVINE: Thank you. It is a real pleasure to be here, and I want to thank the agency for convening this meeting of stakeholders. I suspect that my comments are certainly congruent with everything that Mary has said and I know with almost everything that has been said today.

I am here today actually in two roles, one on behalf of RxHealthValue, a coalition of consumers, health care practitioners, purchasers, and health plans, who have come together to sponsor research, educate the public, and recommend public and private sector solutions to assure that consumers realize the economic and health value of prescription drugs.

I am also here as a prescriber. I have practiced pediatrics for 25 years with the Permanente Medical Group in California and represent the more than 4,000 Permanente physicians in our Medical Group who participate in the Kaiser Permanente Pharmacy Program in Northern California and care for 3.2 million Northern Californians.

Collectively, the members of RXHealthValue represent about 135 million Americans whose vital

interests rest in securing value for the resources they spend on prescription drugs, whether that spend be through deferred wages, public and private health insurance, or direct purchase.

Our concern in RxHealthValue and my concern as an individual physician is that without adequate funding in the future, the food and drug agency, the FDA will not be able to fulfill its most critical public health duties, and its public health duties extend from the very beginning of the process; that is, the integrity of research, the quality and safety of the manufacturing facilities, the robustness of post-marketing surveillance, looking for adverse drug events after the launch of a drug, and the rigor of oversight of promotion to physicians in advertising to consumers.

It is critical for the FDA to have the resources to do that in order for prescription drugs to do what they are designed to do, with the least possible risk to those of us, to all of us who will ultimately use prescription drugs.

As a coalition, we are terribly concerned that the rapidly evolving and growing need to assure patient safety and drug availability is clearly, as Theresa has said, outstripping

available funding.

The vital public health functions performed by the FDA are of value to every American and are going to increase significantly as prescription drugs continue to play an increasing role in health care. Increasingly, prescription drugs are the mainstay of the therapeutic interventions available to the physicians who care for all of us.

Last week, we were pleased to see that the Congress passed and the President signed legislation that actually provides the agency with a budget that includes more money than the agency asked for, and this is a great first step, but I think it is critical to remember that this is only a first step. And we urge the administration in its budget proposal for fiscal year 2003 to propose an increase that would put the agency on a path similar to what happened with NIH in the '90s that would lead it to doubling the appropriations for the FDA by the end of the decade.

We believe that this is absolutely critical for the FDA to fulfill its much-needed and often under-appreciated public health responsibilities. If this were actually to occur,

the FDA might be able to have sufficient resources on a predictable basis to do without user fees, which certainly would be the preference of RxHealthValue's members, but as Mary said, I think we have to be realistic about the environment in which we are living at the moment and it is really unlikely that that increase will be proposed, or if it is proposed, that Congress will enact the taxes necessary to meet this.

PDUFA appears to be a fact of life for us, at least for the immediate future. Given that, it is absolutely essential that the distribution of efforts within the agency not be distorted by the funding. We are concerned that the goals established under PDUFA have forced the FDA to redirect resources for many of its vital functions for review of new drug applications.

I think what we need here is a change in frame. New drug review, as is in the statute, which is defined as processes for the review of human drug applications, begins with the release into the market of a new drug. It doesn't end there. Things like post-marketing surveillance and compliance activities such as regulation and oversight of promotional materials to physicians

and direct-to-consumer advertising are an essential part of new drug review, and the work begins with release into the market. It doesn't end there.

PDUFA only allows user fees to support the narrow piece of the review of new drug applications. The agency, responding to manufacturers over the last number of years, as Theresa's slide showed, has devoted increasingly significant resources to consulting with manufacturers during the discovery and development phase, so that new drug applications meet all requirements. I think your performance has been outstanding, almost a 30-percent increase in successful applications coming through the FDA.

Manufacturers, in effect, are depending on the FDA as if it were a consulting firm. One can imagine the cost to the manufacturers of paying private consultants for the same technical support and advice that is increasingly being provided as a service by the FDA, and we would recommend that you look at the process of formalizing your capacity to provide this assistance to manufacturers, beyond your regulatory obligations, and then those manufacturers that choose to take advantage of it would actually pay for it on an as-needed basis.

Similarly, it is critical for the FDA to continue the excellent work it does, to have adequate technical expertise to review rapidly developing new technologies that are used in drug development in the private sector.

The FDA has maintained a scientific program to ensure that physicians, pharmacists, and other staff have the technical expertise and support that they need to respond to new developments. If appropriated funds are not sufficient, what we could consider, certainly, is financing this kind of activity our of user fees because it is part of the new drug review process.

Driven by the demands of PDUFA, the FDA now acts on new drug applications with great speed and under considerable pressure. This can result in inadequate clinical experience, and I say this as a clinician, with new drugs before they are introduced into the market, driven by massive promotional efforts to physicians and the ubiquitous direct-to-consumer advertising that has appeared since the loosening of restrictions in 1997.

The speed with which many of these drugs are adopted in the prescriber community has been

greatly accelerated compared to the past, and we have got some startling examples of that since 1997.

This one-two punch, faster approvals with less clinical information and more rapid market uptake, means that to maintain the same level of public safety that we have come to expect, more resources, not fewer, must go towards these increasingly important FDA responsibilities of post-marketing surveillance and oversight of promotional activities. Under current law, as you all know, user fees may not be used for these purposes. Congressional appropriations have clearly been inadequate to finance the scope and depth of these activities.

RxHealthValue's core mission is to ensure that Americans have affordable access to health-improving medications. Our members have adopted a consensus recommendation to the FDA regarding the necessity for improvement of post-marketing surveillance and the importance of oversight of information provided both to physicians and consumers. The prescriber community and the consumer community today is dramatically handicapped by the absence of credible independent

third-party information, a base on which they can base prescribing and utilization decisions.

Clearly, we strongly believe that user fees, if we are going to live with them, could be expanded if we look at what the definition of new drug review is to cover these kinds of activities.

The questions posed to this panel specifically were about flexibility, priority-setting, and the question that I think I have addressed which is how can PDUFA goals be met if there continues to be a funding shortfall, I think the short answer to that is PDUFA goals need to be redefined to be much broader.

The FDA must have the ability, the flexibility to balance the competing demands as they see them to ensure the public safety around prescription drugs. That being said, responding to a funding shortfall is something we all live with, and it is never easy. The notion of review priorities where some group or individual determines that certain new drugs have potentially greater health value than others is appealing and would clearly require the wisdom of Solomon.

I would urge the FDA if it pursues this approach to involve at every level of consideration

groups representing patients, providers, purchasers of health benefits and health plans.

We would suggest that the agency attempt to make any prioritization decisions with the question of health value in mind. Applications for drugs to treat now ineffectively treated life-threatening or seriously debilitating conditions should be viewed as the highest priority, and I think we would all agree with that.

In contrast, so-called line extensions intended to preserve manufacturers' market share in the face of patent expiration or loss of market exclusivity should be much lower priority. Active metabolite products like esomeprazole, combinations of generics like metformin/glyburide, extended release products like the slow release metformin are just not as important to the consuming public as drugs for conditions that are currently untreated.

Continuing input from stakeholder groups is going to be essential if priorities need to be established, and the FDA has a long and distinguished history with advisory groups. I would argue that this is a fruitful path to pursue.

One final comment. Probably more germane

to the FDA's overall mission than to PDUFA, I think it is critical that policy-makers realize that outside the Beltway and outside the policy community, there is an enormous gap between what the FDA's mission is and what my colleagues, physicians and consumers, actually believe it is.

Patients and providers think the FDA is working not just to determine that a drug is safe and effective compared to placebo, but that the drugs that you approve are safe and more effective than others you have previously approved. As the administration develops a proposal to submit to Congress next year, I would urge you to consider seeking a broader mandate from Congress, a mandate that would actually fit with what the public believes you are currently doing. It will take more resources, and it will take more information from manufacturers and a different kind of information that will enable prescribers and consumers to actually make judgments about the relative effectiveness of drugs available to treat therapeutic indications.

I want to thank you for the opportunity on behalf of those whom I represent to present at this hearing.

MR. BARNETT: Thank you.

Diane Dorman.

MS. DORMAN: I first want to thank the FDA for giving NORD the opportunity to, once again, talk about PDUFA.

By way of background, NORD participated in FDA's meeting last September and also testified before the House Energy and Commerce Health Subcommittee last May to express our views on the effectiveness of FDAMA. NORD is also an active member of the Patient and Consumer Coalition and also RxHealthValue.

One of NORD's primary goals is to promote the development of new treatments and the cures for rare diseases and to make these therapies accessible to patients. Under the Orphan Drug Act, a rare disease is defined as a health condition that affects fewer than 200,000 people in the United States.

Keep in mind that there are more than 6,000 rare disorders, cumulatively affecting an estimated 25 million Americans. NORD's mission, therefore, is enormous and very much reliant on the successes achieved by academic scientists, pharmaceutical and biotechnology companies, medical

device manufacturers, and most of all the FDA, which regulates these entities.

In the 10 years prior to 1983 when the Orphan Drug Act was passed, only 10 products were developed for rare diseases, and that is why Congress established the Office of Orphan Product Development and provided money for the Orphan Product Research Grant program to provide funding for critically important clinical trials on new orphan drugs, devices, and foods for rare conditions. These treatments have small potential markets and would not otherwise be attractive to the commercial sector.

Today, FDA has approved 220 designated orphan products, proof positive that cooperation between academic researchers, the private sector, the patient community, and the Federal Government can create breakthrough treatments for life-threatening and crippling diseases.

I bring this to your attention only to demonstrate that the FDA with support of all stakeholders, not just industry support, can, and must, continue to, first and foremost, do no harm.

There is a perception by some that the agency is beholding primarily to the drug industry

and continues to play roulette with the lives of patients nationwide. All one has to do is read the headlines to understand how much of the public, including patients and doctors, have lost a certain degree of faith in the FDA's ability to protect and enhance the public's health.

This is not to say that we want to revert back to the good old days when desperately needed therapies took years to reach patients. To the contrary, we all want to see the agency thrive. We all want to see the agency properly and sufficiently funded so it can speed the approval of safe and effective treatments to the American public, but it is this perception of sleeping with the enemy that continues to cloud the agency's representation. A feasible balance must somehow be reached and achieved between speed of approval and safety.

A colleague of mine likes to say sunshine is the best disinfectant, and I couldn't agree with him more. Decisions affecting the health and well-being of patients must no longer be made behind closed doors. Transparency in the approval process must be achieved if the FDA is to regain the complete trust of the patient community.

Before outlining NORD's position on PDUFA reauthorization, I do have a couple of points that I would like to make regarding PDUFA as it relates to the rare disease community.

Written into the user fee regulations is an exception for designated orphan drugs. The language reads that a human drug application for a prescription drug product that has been designated as a drug for a rare disease or condition pursuant to Section 526 shall not be subject to a fee under subparagraph (a) unless the human drug application includes an indication for other than a rare disease or condition.

Regulations go on to say that in order to qualify for this exemption, a company or entity must qualify under the fee waiver or reduction for small business. At the moment, FDA--and I quote--generally considers an entity with less than $10 million in annual gross revenues and no corporate parent or funding source with annual gross revenues of $100 million or more is less likely to be able to continue to provide products that benefit the public health and develop innovative technologies because of user fees.

First and foremost, NORD and the rare

disease community would like assurances from the FDA that during PDUFA negotiations, this exemption is not going to disappear. That is very, very important.

Secondly, because both CBER and CDER have a financial stake in the decision to allow an exemption or not, we believe these decisions would be best made by a more independent entity and consult in consultation with FDA's Office of Orphan Product Development. Without this exemption, many small and startup companies would be unable to bring vitally needed orphan products to market.

Thirdly, because no allowance was made for inflation and because the $10 million and the $100 million are based on '93 figures, the rare disease community will advocate for an increase in the small business exemption as it relates to orphan products, with an inflation index included.

In my written remarks, I have included several examples of some of the problems that have been realized by some of the very small companies developing products for orphan diseases. So I won't go into them now, but I will make one point in my comments. I made mention of Elliott's Solution B as having revenues of $500 million. It

is only $500,000, and I apologize. So, if someone would make note of that, it is quite a huge difference.

DR. WOODCOCK: Too many zeroes.

MS. DORMAN: Yes, too many zeroes.

Although revenues in excess of $10 million may sound substantial, development costs are very, very prohibitive for as yet unprofitable or startup companies, and most entities must consider the contribution of each product individually in order to determine if it will be a contributor or a drain on their bottom line.

While the PDUFA legislation attempts to make exceptions in order that development and commercialization of medications for rare disorders is attractive, the issues and possible solutions should be given serious consideration as future legislative approaches are explored.

Now I would like to go into the first part of question three, which is how can the FDA ensure that PDUFA goals are met if there continues to be a funding shortfall.

It is evidence that PDUFA goals will continue to be met now and into the future, much to the detriment of other critically important

programs established to protect the public health. According to a statement made by an FDA official earlier this year, PDUFA-related program funding has risen 27 percent. It is only the non-PDUFA programs that suffer. Funds are being siphoned from essential programs such as post-marketing surveillance, health fraud investigations, inspections of IRBs, enforcement, training, management, staff retention, advertising enforcement, and adverse event reporting, to the tune of 20 percent in order to meet the letter of the law. This erosion from what I understand has created a $200-million shortfall for these programs over the past 10 years.

As a matter of principle, NORD continues to oppose the concept of user fees with its inflexible performance goals and triggers. However, given the current political and economic climate, it is safe to assume that Congress will not fully fund the FDA sans user fees.

I would like to congratulate Congress, however, for their recently taking that first big step to increase funding for the agency. We feel that is very, very important.

DR. WOODCOCK: Baby step.

MS. DORMAN: Baby step, yes.

Just as the NIH has enjoyed record funding, the agency should also see a doubling of its budget in order to fulfill its increasingly important public health responsibilities, but whatever the solution, whether it is increased user fees, requiring user fees at the earliest phase of development or expanding the use of user fees outside of the new drug approval process, a creative solution to this dilemma must be found.

With the mapping of the Human Genome and the increasingly complex biologic and chemical compounds being developed by industry, the United States will remain in the forefront of medical discovery if, and only if, the FDA is given necessary resources to fulfill its mandate.

Part two of that question, drugs for serious and life-threatening disease require different risk benefit calculations. They should be reviewed more quickly and considered for marketing as early as possible because those suffering with life-threatening diseases or those with no satisfactory alternative treatment options, especially those with untreatable rare orphan diseases, will more often than not accept the risk

a new drug might pose in exchange for the benefits it might well provide.

The FDA should take all steps necessary to ensure that effective new drugs are made available to patients with these serious and life-threatening conditions as soon in the development process as possible.

However, in recent years, it appears that the agency has rushed too many "me, too" drugs through the priority process when they should have been given standard review. We urge the agency to change the way it categorizes standard and priority reviews.

We believe the overriding success of the agency must not be measured by the speed of its work, but by the completeness and scientific soundness of its work in order to protect the health and welfare of the American public. A one-size-fits-all approach must not be taken.

FDA reviewers should be given the latitude to review new drug applications at a slower rate if it is deemed scientifically or ethically necessary, especially when a drug is not a life-saving therapy.

It is obvious to me that some of the drugs

removed from the market in recent years might have been approved with more adequate labeling if FDA had taken the time to recognize adverse events and had required appropriate labeling when the drugs were first approved.

As far as part three of the question, we agree most definitely that the FDA must be able to adapt to the changing market place. Stringent appropriation triggers should not obstruct the agency's ability to efficiently and effectively pursue the goals of ensuring that safe and efficacious products are brought to the marketplace. As currently written, performance goals and mandatory deadlines do not allow for this flexibility.

I thank you very much for giving me the opportunity to speak.

MR. BARNETT: Thank you.

Mike Warner.

MR. WARNER: Thank you, and I will echo my changes to the agency folks for giving us the opportunity to testify this afternoon.

I am Michael Warner. I am vice president for Bioethics at the Biotechnology Industry Organization, or BIO. We represent more than 1,000

biotechnology companies and academic institutions in all 50 States.

Just so you appreciate who we are, more than 90 percent of our members are involved in finding new therapies for currently unmet medical needs, like Alzheimer's, Parkinson's, various cancers, heart disease, and diabetes, and the vast majority of our members have no revenue and have no products currently on the market.

Let me address one thing which one of my colleagues brought up and say, first off, our relationship with the FDA is strictly professional. The biotech industry and FDA are not partners. We are not colleagues. Sometimes we are not friends. Our relationship is arm's length, and we view it as one between scientific peers.

I appreciate the opportunity today to speak about the Prescription Drug User Fee Act, or PDUFA. PDUFA III is of enormous importance to our companies, particularly our small emerging companies. Since the statute expires in October of next year, as you all know, it is appropriate to take the time now to assess its successes as well as its shortcomings.

A lot has changed since the statute was

first passed in 1991. Remember that the biotech industry barely existed back in 1991, and now we have an unprecedented number of potential new drugs in late-stage clinical development.

We have set up internal committees of our members to develop suggestions about reauthorization, and we are taking the advice of those who work with FDA on a day-to-day basis. We hope to have detailed recommendations developed shortly, but in the spirit of this public meeting, I can share with you some general comments.

First of all, since its inception, PDUFA has worked. The law has led to reduced review and approval times, which has meant that patients have had access to new therapies and diagnostics and treatments faster. Put simply, the law has both changed and, in fact, saved lives.

PDUFA has also demonstrated that if given the proper resources, the FDA can effectively administer, review approval programs regarding new drugs and biologics. Despite these successes, bio companies have at least preliminarily identified some concerns with the current process, and I will just highlight and speak in general terms of three.

First, despite a trend of reduced review

and approval times over the years, reports indicates that for FY2000, these times, in fact, increased. This is a big concern for our members, again, particularly the smaller companies, and we just need to understand why that happened.

Second, although one of the purposes of PDUFA is to provide the industry with a more predictable review process, there are some who believe that this is not happening. Specifically, there have been complaints of inconsistency throughout the agency, and consistency, predictability, communication from the agency is critical, again, particularly to our small companies. Some of our companies' very existence is threatened by unclear or confused actions at FDA.

Finally, the lack of an FDA commissioner remains a problem. Now, obviously, the commissioner does not review applications. However, the agency needs a strong leader who can provide direction to the various departments and, importantly, who can fight for additional resources for the agency. We hope to discuss these and other issues with policy-makers over the coming months.

Let me talk about resources for just a

second. The PDUFA reauthorization debate from our perspective provides an opportunity for a broad discussion about FDA resources, not just user fees, but the big issue, the larger issue of FDA resources. It is a given that our industry needs a talented science-based FDA. Indeed, commercial acceptance of our products depends upon a rigorous and thorough review process. The FDA must maintain and remain the gold standard for the rest of the world. We are very fortunate in this country, I think, and all of us recognize it, to have an agency such as the FDA, and we need to make sure that it has the resources it needs so that it can remain the gold standard.

This is going to become even more essential in the coming years as our companies develop scientifically complex products designed to treat formerly intractable diseases, and simply put, we need to ensure that FDA has the resources it needs to do its job.

User fees provide one source of revenue, and BIO has worked hard in the last few years to help increase the appropriation from Congress to FDA. And we intend to do that again next year. Reduced appropriations clearly will seriously

impair this critical agency's abilities.

The biotech industry's strict arm's-length relationship has resulted in more than 100 biotech drugs and vaccines reaching patients. These medicines have now helped more than 270 million people worldwide. In the coming years, we can and must do much more because patients are depending on us.

At BIO, we look forward to fruitful discussions with policy-makers, patients, and the public to create a PDUFA program that ensures that we can all get the drugs, biologics, and treatments that we need.

Thank you.

MR. BARNETT: Thank you.

We are going to do three things now. First of all, I am going to open the floor to comments about this particular issue, which was the financial aspects of PDUFA. Then, after that, I am going to call upon a couple of organizations that registered in advance to speak, and then, finally, I am going to open the floor again for anybody who has any questions or comments about PDUFA that were not covered by the panels.

So, first of all, anybody with any

questions or comments on the subject of this panel which is the financial?

[No response.]

MR. BARNETT: False alarm.

FLOOR QUESTION: I guess this is not totally on the subject.

MR. BARNETT: Would you identify yourself.

FLOOR QUESTION: I am Sandy Marts [ph] from the American Medical Association.

MR. BARNETT: Thank you.

FLOOR QUESTION: This is not totally on the subject, but I noticed a number of the people who have come up to ask questions are reporters and people like that. I would just want to make sure we don't go too far in the direction of trying to say all the other things the FDA does besides new drug approvals are not effective.

I know that I approve a lot of letters that go out from AMA that talk about the things FDA has done on keeping the blood supply safe and also keeping it adequate, antimicrobial resistance, trying to work on problems of drug and vaccine shortages. So, although FDA funding does need to be increased, a lot of what they are doing that are separate from PDUFA that are separately funded, are

really very effective, and they are going a very good job. So I just want to point that out.

MR. BARNETT: Thank you.

Anyone else?

[No response.]

MR. BARNETT: Okay. We have one group that has signed up to speak in advance. It is the Colorectal Cancer network. We have Priscilla Savory. Is she here? Priscilla Savory?

[No response.]

MR. BARNETT: Not here. Okay.

Another one was the Tufts Center for the Study of Drug Development, Chris Milne.

Chris?

DR. MILNE: I want to thank FDA for this opportunity to speak, and I apologize to the panel. I have been told I can turn the mike around and kind of work the audience Sally Jessie Raphael style. So I am going to do that.

MR. BARNETT: You can even take it out and wander around.

DR. MILNE: Well, I don't know. I don't want to make it too sort of theatrical, but I do have some slides today that will hopefully address some of the issues that have come up in the

discussions with all three panels.

I will talk a little bit about the Tufts Center. We are responsible for that figure recently released about the $800-million cost of drug development. Hold your jeers and heckling to the ned. Head-nodding and head-shaking is okay, but I don't want to spend the time I have talking about that particular figure. It is an important figure that does impact on this area, but we have other things to talk about.

The Tufts Center has been studying this area for 25 years. We are, in part, funded by industry, unrestricted grants, but that is all parts of industry, big pharma, biotech, and the software companies that provide services to the industry, CROs, everybody. We also sell products, publications, and we put on courses. So we kind of have an eclectic funding base, if you will.

I think we should remember there are a lot of stakeholders involved in PDUFA companies, also patients certainly. Congress and FDA, we are all stakeholders in this, and you can read the intentions of PDUFA I, which I think have largely been met.

PDUFA II wanted to continue PDUFA I's

success, and then it had some additional emphasis on clinical development. There is not only the approval phase that we have to worry about, but certainly the clinical development phase when we are looking at getting drugs to patients faster. I think that is where there has been a little bit of a--I don't want to say a problem, but some impacts that we might want to point out during this little discussion.

I am going to run through a couple of these slides because there is a limited amount of time, and I know we all want to get to the general discussion. I am going to focus on a couple of the data slides.

This slide is similar to the next few slides you are going to see. So I am going to spend a little time on it. This gets to, again, one of the issues companies are a stakeholder in this. PDUFA I and PDUFA II were supposed to shorten approval times as well as clinical development time. What you see there is the IND phase. It is the clinical development time, and the NDA phase is the approval time. The total phase is, of course, a combination of those two.

You can see by comparing the three columns

in each section there sort of a pre-PDUFA period, that white column. The blue column is then that first performance goal period, 1994 to 1997, with performance goals not starting until '94, and then the most recent PDUFA II period. So you can see sort of a nice staircase of improvement, if you will, as far as decreasing times for approval and even clinical development time decreasing.

There is a little bit of a problem in the NDA phase where you start to see a flattening-out between the PDUFA I and PDUFA II period.

That was for priority drugs. As we get to standard drugs, you see less of that staircase of improvement, if you will, in the shortening of the times of getting those drugs to patients, and a little more flattening out again in that approval phase in that middle set of columns there, but, still, overall there is a shortening of the time from PDUFA I to PDUFA II of the total development time.

For CBER--again, these are drugs going to CBER. These are biological products, rather, going to CBER. Again, it is a little bit harder to see what is going on here, but, certainly, it looks like in the most recent period, '98 to 2000, you

have some increased clinical development time going on, even an increase in the approval phase for priority drugs, leading to a total development time that is increased from PDUFA I to PDUFA II. That is for priority drugs. Again, the criteria in CBER-land is a little more stringent for priority drugs. They have to in addition being an advance over currently marketed drugs, they have to be for serious and life-threatening diseases, more challenging obviously.

Again, for standards, you don't see the staircase, and I have the direction as sort of a bumpy platform. It is hard to tell what is going on here exactly. There is a little bit of a decrease in the overall total development time from PDUFA I to PDUFA II. So talking about that balance that Theresa Mullin discussed, getting back to that balance of making sure that we are going to fulfill the goals of PDUFA I and PDUFA II and PDUFA III, getting back to, again, the important goal of getting markets out to market more quickly.

But, overall, there has been a positive impact over the 10-year period. The PDUFA formula, if you will, has worked. Looking at that first column, increasing FDA staff has resulted in a

22-percent decrease in clinical development time, a halving, if you will, of approval times, and at the same time an increase by 33 percent of applications overall being approved.

Now, part of the problem, perhaps, with the PDUFA II period has been these additional resources that had to be devoted to some of these FDAMA activities, drawing on some of the same personnel. In addition, there is also the emphasis to try to reduce that clinical development time by focusing on helping the industry to address certain issues with clinical holds and other clinical development issues, having meetings at critical junctures during clinical development.

In addition, it talked about some new programs that had demanded a lot of resources from FDA, the pediatric exclusivity program, as well as the fast-track development program for serious and life-threatening illnesses. We have heard mentions of that already. This is just a quick summary of how beneficial and critical these programs are, but they do demand resources.

So far, just in the 3 years that the pediatric program has really been in full swing, they have labeled 20 active noieties, 4 pediatric

indications, and a third of those, they found significant differences, significant new information with regard to dosing and adverse effects. They were probably being used incorrectly, if you will, or not as appropriately as they should have been in the off-label world.

Again, over 70 diseases are being addressed, 500 studies are in progress. Thirty-two percent of those are in, according to a survey that we did, in neonates and infants, very difficult subpopulation to address, again, dozens of formulations and biological sampling technique and clinical endpoint improvements. They are advancing the science of pediatric clinical trials.

It is not coming cheaply. Our survey indicates that it is costing industry about a billion dollars to handle these 250 requests. So, again, there is some expense on that side as well, certainly, along with FDA, and we are going to see that in the next slide.

FDA. They have had 65 staffs spread over 13 pediatric activities. They have also had other things that they have to do during this period in addition to now. We have the bioterrorism and some other activities going on. They have been spread

very thin in that regard. They have the new office of Pediatric Development. That is good, but, again, stretched resources, and they have had to do this while there has been a doubling of pediatric supplements to review by that same review division personnel that we talked about that do your typical drug development review processes.

Fast track, also, a tremendously beneficial program. We followed 65 of the first fast-track designations that we could get public information on. Of those, we found that 40, just from the information we could gather out in public sources, were breaking new ground. Frontiers of science handling refractory disease, diseases that have no other treatment, diseases for resistant organisms, novel approaches to diseases, again, very challenging, a very challenging program not only for developers, but certainly for FDA to have to assist, give consultation on development, and also to review those drugs.

You see that there has been some benefits already, just in the half-dozen or so products that we have been able to identify as having been all the way through the process that we could get, developments times are looking at those gray bars.

You can see that the clinical times and the approval times have been tremendously decreased or those fast-track drugs. That is why they call them "fast track," hopefully.

Given that total development time for this small cohort, it is less than 4 years from the time they submit their IND to the time they get approval. It is out on the market, less than 4 years. That is really terrific news to patients that are waiting for desperately needed drugs.

Again, it doesn't come without its costs in terms of resources, again, not only for industry, but certainly for FDA. This is not a small program, 170 designations in about, again, 3, 4 years, five- to six-fold increase in the number of meetings that typically a fast-track sponsor will have compared to other sponsors. That is a lot of agency time. That is a lot of industry time. The agency might have to have 10 to 20 personnel involved in these formal meetings, again, tremendous resource drain.

Reviewing clinical time would also be challenging because we are dealing, again, at the frontiers of science, serious and life-threatening illnesses, 30 or 40 of them, in populations that I

call vulnerable because there is very little clinical trial data offered on some of these children. Even women, typically, were not involved in clinical trials, a lot previously, the elderly, and 50 percent are for patients with rare disorders. You heard about them as far as the Orphan Disease Act is concerned and the implications for that program.

Overall, conclusions, the intent of PDUFA I largely has been fulfilled, I believe. Again, they have to get back to that balance that was intended to occur in PDUFA II and PDUFA III hopefully will get that balance back.

There is a perspective on safety that has to be considered. We don't want to sacrifice public health, certainly, in this process. I don't see that the evidence indicates that there has been a sacrifice of that yet. Certainly, that doesn't mean that should be any complacency.

We looked at the data and we saw that from 1980 to 1993, the pre-performance goals cohort of drugs that were approved during those years, we found a 3.2 percent withdrawal rate for safeties, with about 4.6 years on average occurring before from the time that drug was marketed until the time

that drug is withdrawn, looking at the post-PDUFA era out to the performance goals--were implemented. You can see that the withdrawal rate is fairly similar, 3.4 percent, and there was actually a shorter recognition time, if you will, time from when the drug was approved until it was actually recognized as being problematic and withdrawn.

Again, no recent for complacency. Lots of work has to be done. It is a much more challenging environment. More drugs are out there on the market, in the U.S. market first. We identified that as a problem. Also, these are more challenging drugs. You have many more people involved in the development process now, many new players, different types of approaches being taken. Certainly, it is a very important time to increase post-marketing surveillance. There are just limits to pre-market testing.

You can, to some degree, take those into account by increasing your risk management and your post-marketing, but, in general, the overall program has to be brought back into balance by pouring more resources not only into bringing back the advancements that were made in approval and review times, but also in addressing some of these

new concerns and challenges that are out there.

Thank you.

MR. BARNETT: Thank you, Dr. Milne.

Anyone on the panel want to comment on this?

Yes.

MS. LEVINE: Yes, just a couple of things. I think we are using the word "balance" in two different ways. I think the panelists have been talking about balance between new drug review and the other public health activities that the FDA engages in on behalf of the consuming public, and I just want to talk about the issue of decrease and development time for just a second.

I think with drugs, with prescription drugs, speed is not necessarily life. While it is true that 3.2 percent and 3.4 percent look like they are almost the same, the actual numbers are significantly different because they are a percentage of a different multiplier.

The reason, I believe, of the shorter recognition time is because the clinical trials are continuing with a shorter development time and a rapid uptake after introduction in the market. What we are seeing is essentially a clinical trial

that is continuing under less than ideal circumstances, and we are getting information, fortunately, but not perhaps in the best way possible.

The other issue for me that is raised--and this is not the subject of this panel--by the dramatic decrease in development time is that patent life, effective patent life is related to historical notions about how long it takes to get a drug through development. So, if we are seeing based on the FDA's good efforts dramatic decreases in development time, somebody perhaps ought to look at whether we have excessive patent life based on a much shorter development cycle.

MR. BARNETT: Thank you.

Any other panelist want to comment?

DR. MILNE: I would like to say one thing about the safety issue. Just looking at something I read in the paper yesterday where they were talking about a report about surgical errors, according to this report, there had been 108 surgical errors in the last 2 years. That would be about 4.5 per month, but they said that in the last month, there had been 11. So sometimes events occur as blips rather than over a nice scheduled

period.

Again, thinking about those 12 drugs that have been withdrawn since 1997, again, only I think 8 of them were actually approved in the PDUFA era, you can't draw too much from that, and, again, you can carve the data a number of different ways. Even if you don't find that that indicates a particular problem, safety withdrawals are only one aspect of the safety issue. Certainly, the warnings and the black boxes and the other things that occur are another issue, and no matter what you find, there is never any reason for complacency. Something that can always be improved is safety.

As far as the balance, yeah, I think we can say that. Perhaps there is a couple of ways to think about balance, and I was using it in a different way.

MR. BARNETT: Thank you.

I think what I want to do now is ask if there is anyone in the audience who has questions or comments on something about PDUFA that was not covered by the panels. If so, now is the time to come on up.

MR. BLOOM: Actually, I have two

questions. I will take a follow-up, just like in the White House.

This question is actually for Dr. Woodcock and Dr. Zoon. One of the things that strikes me is that I would like to hear a little bit about the appropriateness of having the same performance guidelines and the same time parameters for applications that go to CDER versus CBER because it seems to me that the difference in the quality of applications and particularly the fact that in one instance you have a thousand companies, small companies, usually not very profitable companies turning in applications versus large pharmaceutical companies with much better resources, longer relationship with the agency, I would imagine the applications, there is probably a great difference in how those applications come into the FDA.

So is it appropriate to have the same goals for both divisions, or does it make sense to have different parameters? How does that affect you.

I know that Dr. Zoon has been quite candid at previous meetings stating quite frankly that PDUFA has created a sweat-shop mentality at CBER, and I am wondering if the two of you would comment

on that, please.

DR. ZOON: I think you raise a very important point. I think the diversity of the different sponsors that the Center for Biologics works with is quite great, and I do think there is a lot more help that smaller companies or sponsors need because they are less experienced in drug development and product development. And it does require extra support and help to get them through the process.

It also many times can affect the quality of the applications that are submitted to the agency. So I do think that communication is extremely important for the small companies, and especially if they don't have a lot of experience in drug development. My sense is we can talk about whether the goals should be the same or not.

The other thing that I think is important to recognize, that many of our sponsors are at the cutting edge of technology, and having to have the proper science base for the agency to deal with novel technologies is also very challenging for the Center for Biologics and has been something that we have struggled and tried very hard to support the science base because, if you can't understand the

technology, you can't very well regulate it well. I think part of our efforts, really, to try to make sure that our scientists are best prepared to work with the industry scientists to very best understand the products and often were having the right policy and guidance during the actual review of products because these are new and have never seen the light of day. So I think all of those things do make a complex situation.

I think it is a legitimate question. I think some analyses would need to be done in regard to that, to look at what the issues are surrounding it and how that should be approached, and I also think many of the things that we do will continue to challenge the agency with respect to keeping up with the science. So I think that is something that we continue to look forward to working with all segments, both the industry and the public and our academic colleagues and Government colleagues to ensure that we can do a good job.

Thank you.

FLOOR QUESTION: I think that voluntary compliance is an oxymoron. Having spent a lot of time in consumer protection, nothing should be approved until all the information is in. It

should be mandatory compliance. There is this tremendous rush now to get approval of drugs, and maybe if there is a penalty or a cost for drugs that are recalled, there might be a slowing down of trying to rush to get your drug approved.

I also think I have been hearing for a long time about MedWatch and they don't have enough people. Well, in all the years I worked in consumer protection, I had a whole cadre of volunteers working for me, and Washington is filled with professionals who are retired. There is no reason why the FDA cannot use these wonderful retired people, professional people, to help them with MedWatch.

I volunteer now in the State's Attorney's office. So we have a lot of people here who can contribute to society and would love to work in MedWatch, and I have a feeling it won't happen, anyway, but we have to keep reinventing the wheel and we have to use the resources we have and your money doesn't go that far, but I really feel that all information should be available before the drug is approved. It will save you money in the long run. They have to come back with more information and more information. So I don't know, and I guess

I am a little cynical, and I am ashamed to admit it. Is this rush for consumers, or is it rush for profit?

MR. BARNETT: Thank you.

Anyone else?

Yes, come on up. Identify yourself.

FLOOR QUESTION: My name is Mickey Hunt and I am the president of Mickey I. Hunt and Associates, which is a health policy consulting firm based here in Washington.

I would appreciate it if Dr. Woodcock and Dr. Zoon would clarify the criteria that are used to determine whether an application receives a priority review.

I understand there is some difference in criteria between the Center for Biologics and Drugs and also that there are four routes that can be used within the Center for Drugs to qualify for a priority review.

DR. WOODCOCK: A priority review is fairly straightforward. We have had this criterion in place before the user fee program, as you probably know. It relates to something that would provide a benefit above and beyond existing therapies. There have been some issues around that. It is usually

taken up by the expert clinicians in the review division, which is the subspecialty area, who would determine that that therapy would propose an advance. It can be as straight forward as a once-a-day pill. That might seem trivial unless you realize that adherence to medications or lack of adherence is probably the number-one reason that they don't work for people. It is that people don't take the pills. So anything that promotes adherence to your medication is something that really can be an advance for patients, but some folks might dispute that and there is some controversy. It has to be an advance over and above existing therapy.

Often, it is much more of an advance. It would be something that had been shown to have a survival benefit in clinical trials or something that is shown to have some major symptomatic benefit or addressing a disease that doesn't have therapy.

Kathy?

DR. ZOON: I would just most biologics that we deal with, looking at these, many of the drugs and products that we regulate represent new treatments or advance treatments for severe and

life-threatening illnesses for which there have been no other potential therapies. So this has been both the medical advance and safety issues that are also considered in our triaging as well.

Most of them are quite comparable to the Center for Drugs, and I think there are a few minor differences, but they are actually quite overlapping.

MR. BARNETT: Anyone else?

[No response.]

MR. BARNETT: If that is the came, I am going to ask Dr. Suydam if she has any final comments to make before we break.

DR. SUYDAM: I just want to thank everyone for their participation, particularly our panelists. I think we heard lots of interesting ideas, things that will benefit, I think, the process as it moves along. We appreciate your interest. We look forward to working with all of you in the future, and I think that together we can make this program work. And thank you again for supporting FDA to the degree you have. We appreciate it very much.

MR. BARNETT: Okay. Thanks for coming, and speaking of safety, drive carefully.

[Whereupon, at 2:36 p.m., the public meeting was adjourned.]

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